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Best Practice Guideline for Managing Interstitial Cystitis in Adult Women

By

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Bachelor of Science in Nursing
University of South Carolina, 2008

Submitted in Partial Fulfillment of the Requirements

For the Degree of Doctor of Nursing Practice in

Primary Care Family Practice

College of Nursing

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ABSTRACT

Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic disease characterized by symptoms of urinary urgency, frequency, bladder pain, and chronic pelvic pain in the absence of known pathology. Selection of appropriate treatments depended on the severity of the patient's symptoms and patient's preference. This review found that it is important for providers and patients to set realistic goals for symptom improvement when starting a new treatment.

The purposes of this project was to 1) conduct a substantive literature review on treatment guidelines for IC/PBS, 2) analyze the literature for comparing oral pharmacological interventions and behavioral interventions for IC/PBS, and 3) determine the best practice recommendation for the management of ICS/PBS in adult women. An extensive review and analysis of literature published from 2002 through 2012 was conducted to answer the following PICOT question: In women ages 18 and older with a diagnosis of IC/PBS, who are not pregnant (P), how do oral pharmacological interventions (I) compare with behavioral interventions (C) Best practice for managing IC/PBS in adult women ages 18 and older, evidenced by a decrease in IC/PBS symptoms indicated by a reduction in the patient's ICSI and ICPI scores from baseline or patient self reported improvement of symptoms. (T)?

Best practice management of IC/PBS begins by setting realistic goals with the patient for adequate symptom control and quality of life. The literature showed that behavioral modification and adequate coping strategies significantly improve symptoms and quality of life for women with IC/PBS (Chaiken et al., 1993; Rothrock et al., 2003). The literature did not support the use of amitptylene, cimetidine, or hydroxyzine for management of symptoms of IC/PBS in women (Dimitrakov et al., 2007; Hill et al., 2008; Unwin, 2011). RCTs and systematic reviews found that PPS significantly improved symptoms of IC/PBS and quality of life with minimal side effects and the medication was generally well tolerated (Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sand et al., 2008). Management of IC/PBS should focus on providing adequate relief to the patient with the most conservative treatments possible.

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LIST OF ABBREVIATIONS

| | |
|--------------|--|
| ABC | anesthetic bladder challenge |
| AUA | American Urological Association |
| CyA | Cyclosporine A |
| DMSO | dimethyl sulfoxide |
| FDA | Food and Drug Administration |
| GAG | glycosaminoglycan |
| IC/PBS | Interstitial cystitis/Painful Bladder Syndrome |
| ICS | International Continence Society |
| ICSI | Interstitial cystitis symptoms index |
| ICPI | Interstitial cystitis problem index |
| NIDDK | National Institute of Diabetes, Digestive and Diseases of the Kidney |
| PPS | pentosan polysulfate (Elmiron) |
| PST | potassium sensitivity test |
| PUF | Pelvic Pain and Urgency/Frequency questionnaire |
| QOL | quality of life |
| RCT | Randomized Control Trial |
| TCA | tricyclic anti-depressant |
| UTI | urinary tract infection |

INTRODUCTION

Interstitial cystitis (IC) is a chronic disease that is characterized by symptoms of urinary urgency, frequency, bladder pain, and chronic pelvic pain in the absence of known pathology (Heck, 2007). Recently IC has assumed labels such as painful bladder syndrome (PBS); this term was introduced to better describe the symptom complex that patients with IC experience (Forrest & Moldwin, 2008). Current literature refers to the disorder as IC/PBS to avoid any unnecessary confusion (Dell, 2007; Forrest & Moldwin, 2008; Hanno et al., 2011). The typical patient with IC/PBS is a young to middle age adult woman who complains of bladder pain, pelvic pain, urinary frequency and urgency, nocturia, dysuria and dyspareunia in the absence of abnormal findings on a urinalysis (UA) or urine culture (Chaiken, Blaivas, & Blaivas, 1993; Dell, 2007). Thus, IC/PBS is often a diagnosis of exclusion based on clinical findings once differential diagnoses such as overactive bladder, urinary tract infection, endometriosis and chronic pelvic pain syndrome have been ruled out (Dell, 2007; Forrest & Moldwin, 2008).

Traditionally, a cystoscopy is conducted for the diagnosis of IC/PBS. Classic cystoscopic findings include glomerulations of the bladder known as Hunner's Ulcers and bleeding. However, not all patients with IC/PBS will demonstrate these classic findings (Chaiken et al., 1993; Hanno et al., 2011; Theoharides, 2007).

The percentage of IC/PBS patients who have Hunner's ulcers varies from five to fifty percent depending on the sample population studied (Klutke & Klutke, 2008; Rosamilia, 2005). Because cystoscopy findings among patients with IC/PBS vary, current evidence does not support the use of cystoscopy for the diagnosis of IC/PBS (Chaiken et al., 1993; Hanno et al., 2011; Onwude, 2009; Rosenberg & Hazzard, 2005; Theoharides, 2007). Instead, providers are encouraged to identify, assess, and monitor treatment progress using tools such as the O'Leary-Sant interstitial cystitis symptom index (ICSI), the interstitial cystitis problem index (ICPI) and the Pelvic Pain and Urgency/Frequency (PUF) Patient symptom scale (Dell & Butrick, 2006; Hanno et al., 2011; Nickel et al., 2005; Theoharides, 2007). The PUF scale is a symptom questionnaire that is validated for use in diagnosing IC/PBS. A score between 0-35 is used in the PUF scale to rate symptoms, the higher the score the more likely a patient is to have IC/PBS (Parsons, 2006). A score of 12 is considered by experts to be indicative of IC/PBS (Forrest & Mishell, 2009). The O'Leary-Sant ICSI and ICPI have been validated for evaluating symptoms and problems related to IC/PBS in the patient that has already been diagnosed with IC/PBS, these tools are recommended for use in evaluating the effectiveness of treatments, however its validity for use as a diagnostic tool has not been studied (O'Leary, 1998; Theoharides, 2007). These tools are primarily based on symptomology and do not include physical exam findings or treatment guideline parameters.

Currently, 183 treatments have been documented in the management of IC/PBS; no one treatment or guideline approach has been identified as the standard therapy

(Dell & Butrick, 2006; Onwude, 2009; Rosamilia, 2005). Therapies for IC/PBS include oral medications, intravascular medications, physical therapy, electrical stimulation, biofeedback, dietary modifications and surgery (Hanno et al., 2011; Rosamilia, 2005; Theoharides, 2007). Most treatments have not been shown to significantly improve symptoms of IC/PBS; there is no single treatment that has been found to be effective for a majority of IC/PBS patients (Dell & Butrick, 2006; Hanno et al., 2011). Clinical trials have studied management of IC/PBS patients with varying degrees of symptom severity making it difficult for providers to draw conclusions and generalize results (Theoharides, 2007). Selection of appropriate treatments depends on the severity of the patient's symptoms and patient's preference, it is important for providers and patients to set realistic goals for symptom improvement when starting a new treatment (Hanno et al., 2011; Onwude, 2009).

Because of the lack of clear guidelines to aid providers in assessing and managing IC/PBS, it is estimated that many patients are undiagnosed, misdiagnosed, or mismanaged for five to seven years (Forrest & Mishell, 2009; Heck, 2007). Misdiagnosis, delayed diagnosis, and inappropriate management of IC/PBS leads to decreased quality of life and poor outcomes for patients (Forrest & Moldwin, 2008; Heck, 2007). The first healthcare provider that many women with symptoms of IC/PBS are cared for by is not a specialist, but their primary care provider (Patel et al., 2008). In a survey of primary care physicians, Clemens et al. (2010) found that many primary care physicians have erroneous beliefs about IC/PBS, including the belief that IC is caused by a psychiatric illness or and STD. Only 67% of physicians surveyed correctly identified the hallmark

symptoms of IC/PBS and commonly treated patients with NSAIDs and anticholinergics, not recommended therapies for IC/PBS (Clemens et al., 2010). Familiarity with IC/PBS and best practice guidelines assist healthcare providers in achieving better outcomes for women with IC/PBS. The purposes of this project is to 1) conduct a substantive literature review on treatment guidelines for IC/PBS, 2) analyze the literature for comparing oral pharmacological interventions and behavioral interventions for IC/PBS, and 3) determine the best practice recommendation for the management of ICS/PBS in adult women, ages 18 and older.

CHAPTER 1

BACKGROUND AND SIGNIFICANCE OF THE PROBLEM

Definition

IC/PBS is a chronic progressive disease that is characterized by a collection of symptoms including urinary urgency, frequency and chronic pelvic pain in the absence of other explanatory pathology (Heck, 2007). There are several definitions found in the literature. The Society for Urodynamics and Female Urology defines IC/PBS as an unpleasant sensation, described as pain pressure or discomfort perceived to be related to the urinary bladder and associated with lower urinary tract symptoms of more than six weeks duration in the absence of infection or other identifiable cause (Hanno et al., 2011). The National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) developed a set of diagnostic criteria for use in clinical studies of IC/PBS. The NIDDK criteria defines IC as the presence of glomerulations or Hunner's ulcers on cystoscopy, and either pain associated with the bladder or urinary urgency (Forrest & Moldwin, 2008; Hanno, 2002; Hanno et al., 2011; Onwude, 2009; Rosamilia, 2005; Theoharides, 2007). The criteria developed by the NIDDK were developed for research purposes and are considered to be too restrictive for use as clinical diagnostic criteria because it is believed that these criteria do not capture individuals who are in early stages of IC/PBS (Hanno, 2002; Ibrahim, Diokno, Killinger, Carrico, & Peters, 2007; Parsons, 2002;

Rosenberg & Hazzard, 2005). However, due to the lack of definitive diagnostic criteria the NIDDK criteria have been used in the clinical setting (Hanno, 2002). The International Continence Society defines PBS as the complaint of suprapubic pain related to bladder filling, accompanied by other symptoms such as increased urinary frequency in the absence of proven UTI or other obvious pathology (Rosamilia, 2005). Theoharides (2007) defined IC/PBS as symptoms of pain pressure or discomfort involving the lower abdomen and bladder relieved by voiding with urinary urgency and frequency in the absence of a UTI or other identifiable pathology.

Diagnosis

In addition to chronic pelvic pain, urinary frequency and urgency, women complain of nocturia, dysuria, and dyspareunia (Dell, 2007). Many of these symptoms overlap with other disorder; because of this IC/PBS is a diagnosis of exclusion. Differential diagnoses that must be considered include chronic pelvic pain syndrome (CPPS), overactive bladder (OAB), urinary tract infection (UTI), irritable bowel syndrome (IBS), endometriosis and sexually transmitted diseases (STD) (Dell, 2007; Forrest & Moldwin, 2008).

Etiology

The exact etiology of IC/PBS is unknown but several theories have been proposed including that the IC/PBS is caused by autoimmune breakdown, infections, neurologic disorder, and psychological factors (Klutke & Klutke, 2008). The theory that is most widely accepted is the multifactorial theory. This theory purports that there is initial damage to the epithelium of the bladder which leads to increased permeability to

cytotoxic factors resulting in chronic inflammation of the bladder lining (Burkman, 2004; Burrell & Hurm, 1999; Dell, 2007; Forrest & Mishell, 2009; Jamison, Dawson Timothy, & Helfand, 2007; Klutke & Klutke, 2008; Rosamilia, 2005). The initial damage to the glycosaminoglycan (GAG) lining of the bladder can be caused by many factors including infection, childbirth, pelvic surgery, bladder trauma or introduction of toxins to the bladder (Forrest & Mishell, 2009; Klutke & Klutke, 2008). The increased presence of mast cells in the bladder of women with IC/PBS suggests infectious or autoimmune process (Burrell & Hurm, 1999; Jamison et al., 2007). The increased permeability of the bladder epithelium and continued exposure to toxins leads to chronic inflammation and neurogenic upregulation contributing to chronic pain, scarring of the bladder and decreased bladder capacity (Dell, 2007; Klutke & Klutke, 2008).

The average age of onset of IC/PBS is in the mid forties. However, about 25% of patients diagnosed are less than thirty years of age. Recently, there have been some reports of pediatric cases. However, there is scant literature available on pediatric IC/PBS (Hanno, 2002; Heck, 2007). IC/PBS affects both men and women. It is estimated that 90% of the cases of IC/PBS occur in women (Heck, 2007).

Prevalence.

The prevalence of IC/PBS in the general population is a number that researchers have struggled to ascertain. Difficulty in assessing the prevalence of IC/PBS results from a lack of uniform diagnostic criteria, a definitive diagnostic test, the variable presentation of symptoms in the early stages of IC and the overlap of symptoms with other common disorders (Ibrahim et al., 2007; Rosamilia, 2005; Rosenberg & Hazzard,

2005). To further complicate prevalence determination of IC/PBS, researchers have found that the prevalence varies depending on which definition of IC/PBS is used. Forrest and Moldwin (2008) suggested that sixty percent of patients that are diagnosed with IC/PBS by an expert clinician based on clinical presentation would be excluded from the diagnosis based on the strict NIDDK criteria.

Several studies have been conducted to attempt to estimate the prevalence of IC/PBS, using several different definitions of the disorder. These studies have found various prevalence rates of IC/PBS determined by the definition of IC/PBS used in the study design. The RAND Interstitial Cystitis Epidemiology (RICE) study, found that 2.7% to 6.5% of women in the United States over the age of 18 met the symptom criteria for diagnosis with IC/PBS; this translates to approximately 3.4 to 7.9 million women in the United States (Kerr, 2009). The range of prevalence estimates found in this study are due to the use of two definitions of IC/PBS a high-sensitivity definition to estimate the high end and a high specificity definition to estimate the low end of the range (Kerr, 2009).

Rosenberg and Hazzard (2005) conducted a study of women seen in a primary care office for symptoms of IC/PBS such as urgency, frequency, disuria, and pelvic pain. They used the O'Leary-Sant IC symptom (ICSI) and problem index (ICPI) and the Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale to evaluate the prevalence of IC/PBS among their patients. Their findings indicate that using the PUF scale 12.6% of the patient population had IC/PBS, using the O'Leary-Sant ICSI and ICPI only 0.57% of the population met diagnostic criteria for IC/PBS (Rosenberg & Hazzard, 2005). The

researchers conclude that the O'Leary-Sant indices are not designed for screening for IC/PBS but as a tool to evaluate progression of established IC/PBS. The PUF index, validated as a screening tool for IC/PBS, has increased sensitivity to identify patients with IC/PBS (Rosenberg & Hazzard, 2005).

Rosenberg and Hazzard (2005) estimated that the actual prevalence of IC/PBS in women in a primary care setting was between 0.57% and 12.6%, the percentages estimated by using the PUF scale and the ICSI and ICPI. Ibrahim, Diokno, Killinger, Carrico and Peters (2006) conducted their own study to determine the prevalence of IC/PBS using multiple definitions of IC/PBS. Ibrahim et al. (2006) found that using the most restrictive definition the prevalence of IC/PBS in a community population was 3.7%; using the least restrictive definition the prevalence was 17.3%. These researchers concluded with 95% confidence that the actual prevalence of IC/PBS in the general population is between 3.7% and 17.3%. Using their findings, Ibrahim et al. (2007) generalized this data to the population of women in the United States over age 18. They estimated that between 422,803 and 21,454,813 women are affected by IC/PBS annually.

Costs

Estimates indicate that women with IC/PBS pay two to three times more for direct health care cost than the average woman (Stanford, Chen, Wan, Lunacsek, & Sand, 2008).

Successful management of IC/PBS is often difficult. Early diagnosis reduces patient care costs, as IC/PBS is more responsive to therapy in its early stages (Parsons,

2006). Misdiagnosis, under diagnosis, and delayed diagnosis require patients to seek evaluations by multiple health care providers, often leading to unnecessary diagnostic testing, surgical procedures and a decreased quality of life (Forrest & Moldwin, 2008; Heck, 2007; Sand et al., 2008). The chronic nature of IC/PBS necessitates long-term medical management of the disorder and permanent therapeutic regimens to minimize symptoms and improve quality of life (Schmid et al., 2011).

Wu et al. (2006) conducted a study to estimate the average medical cost for patients with IC/PBS in the first year after diagnosis. These researchers found that the average patient spent \$1,572 U.S. on medications in the first year of treatment and \$5,041 during the first year of diagnosis on medical services. The majority of these costs paid for outpatient services (Wu et al., 2006). Within a year, these IC/PBS patients spent approximately \$3,320 more than the control group of patients without IC/PBS (Wu et al., 2006). These values only reflect direct cost of medical care for IC/PBS, not the cost of lost wages due to an inability to work. Wu et al. (2006) found that the indirect cost of IC/PBS in lost wages averages \$726 during the first year of diagnosis.

Quality of life

In addition to increased health care cost, women with IC/PBS report a decreased quality of life (QOL). Stanford et al. (2008) found that women with IC reported a significantly lower quality of life compared to an average woman. Studies comparing the QOL of patients with IC/PBS to women with other chronic diseases found that women with IC/PBS reported lower quality of life than women with rheumatoid arthritis, HTN and chronic kidney disease on dialysis (Rosamilia, 2005; Rothrock, Lutgendorf, & Kreder,

2003). They reported sleep deprivation and increased levels of pain, including dyspareunia. Moreover, they reported depression, suicidal ideation, absences from work, sexual dysfunction, poor family relationships and physical and emotional stress (Burkman, 2004; Heck, 2007; Rosamilia, 2005; Stanford et al., 2008). In short, the unpredictable nature of the disease and symptom flares cause debilitating pain, urgency and frequency that restrict patients to the restroom, limiting participation in social activities (Rothrock et al., 2003; Warren, 2007). Many women with IC/PBS experienced anxiety and depression related to their symptoms, misdiagnosis, delayed treatment, and medical costs (Clemens et al., 2010; Forrest & Mishell, 2009; Wu et al., 2006). Studies found that with appropriate disease specific treatment, QOL in women with IC/PBS significantly improved (Clemens et al., 2010; Forrest & Mishell, 2009; Sairanen et al., 2009). Forrest and Mishell (2009) as well as Sairanen et al. (2009) recommended using quality of life indicators to evaluate effectiveness of treatment regimens for IC/PBS.

Co-morbidities.

Women with IC/PBS often have other co-morbid medical conditions that contribute to many of the symptoms that the experience with IC/PBS. These included allergies, fibromyalgia, inflammatory bowel disease, high tone pelvic floor muscle dysfunction, endometriosis, vulvodynia, chronic pelvic pain syndrome, UTI, depression and anxiety (Hanno, 2002; Panzera, 2007; Parsons, 2006; Wu et al., 2006). Control of co-morbid conditions can improved IC/PBS symptoms. Parsons (2006) found that over seventy percent of patients with IC/PBS also experienced environmental allergies. One theory regarding the etiology of IC/PBS was that damage to the lining of the bladder is

related to an allergic response (Burrell & Hurm, 1999). Control of allergies in women with IC/PBS improved IC/PBS symptoms. Hydroxyzine was especially useful over other antihistamines because chronic use suppressed degranulation of mast cells (Parsons, 2006). A high percentage of women with IC/PBS also experienced depression; treating depression in women with IC/PBS with amitriptyline improved depressive symptoms and decreased pelvic pain associated with IC/PBS (Hanno et al., 2011; Parsons, 2006; Wu et al., 2006).

Patient outcomes.

IC/PBS is a chronic disease with no known cure; management was targeted at relieving symptoms and maximizing quality of life (Dell & Butrick, 2006; Forrest & Mishell, 2009; Nickel et al., 2005). Negative outcomes for women with IC/PBS were associated with debilitating pelvic pain and urinary frequency, which progressively worsened over time (Panzera, 2007; Rosenberg, Newman, & Page, 2007; Wu et al., 2006). The adverse outcomes associated with IC/PBS varied and included sleep deprivation, travel and diet restrictions, avoidance of sexual intercourse, sexual dysfunction, poor social functioning, decreased mental health, depression, poor family relationships and an inability to work (Ibrahim et al., 2007; Panzera, 2007; Rothrock et al., 2003; Wu et al., 2006).

Many patients faced occupational limitations due to symptoms of IC/PBS (Rosenberg, Newman, et al., 2007; Stanford et al., 2008). Over fifty percent of patients with IC/PBS were unable to work full time (Hanno, 2002; Rothrock et al., 2003; Wu et

al., 2006). Ibrahim et al. (2007) reported that patients with IC/PBS were less likely to work full time and more likely to be disabled or unemployed.

Women with IC/PBS were more likely to be diagnosed with depression, over half of IC/PBS patients reported depression related to urinary symptoms and sexual dysfunction (Bogart, Suttorp, Elliott, Clemens, & Berry, 2011; Rosenberg, Newman, et al., 2007; Rothrock et al., 2003; Wu et al., 2006). Women with IC/PBS were less likely to seek treatment for their depression due to stigma related to talking about urinary disorders and sexual dysfunction caused by symptoms of IC/PBS (Bogart et al., 2011; Rosenberg, Newman, et al., 2007; Rothrock et al., 2003). Sexual dysfunction was common among women with IC/PBS, and can took many forms including dyspareunia, symptom flares after intercourse, decreased sexual arousal and decreased orgasm frequency (Bogart et al., 2011). Bogart et al. (2011) found that eighty-eight percent of women with IC/PBS reported at least one symptom of sexual dysfunction, compared to forty-three percent of women in the general U.S. population. Sexual dysfunction led to lack of intimacy and poor family relationships (Bogart et al., 2011; Rosenberg, Newman, et al., 2007). Approximately, seventy percent of IC/PBS patients reported disruption in their family relationships and responsibilities due to symptoms of IC/PBS (Rothrock et al., 2003; Wu et al., 2006).

Purpose

The purposes of this project was to 1) conduct a substantive literature review on treatment guidelines for IC/PBS, 2) analyze the literature for comparing oral pharmacological interventions and behavioral interventions for IC/PBS, and 3)

determine the best practice recommendation for the management of ICS/PBS in adult women.

Management of IC

Health care providers were inconsistent in diagnosis and treatment of IC/PBS, and many did not recognize the disorder early enough in most patients to effectively manage the disease (Forrest & Mishell, 2009; Hanno et al., 2011; Heck, 2007). The diagnosis of IC/PBS was difficult due to the lack of specific histopathologic changes, unpredictable flares and remissions of symptoms early in the disease progression, and an extreme variability in presenting symptoms among patients (Dell, 2007; Hanno, 2002; Hanno et al., 2011). It was estimated that the delay in diagnosis from onset of first symptoms is between five and seven years (Heck, 2007; Rosamilia, 2005). Early recognition and initiation of appropriate treatment is essential to improved QOL for women with IC/PBS. IC/PBS was shown to respond better to available treatments if recognized early. Many treatments have better therapeutic response if initiated during the first two and a half years of symptom onset and response improved over the duration of treatment (Forrest & Mishell, 2009; Forrest & Moldwin, 2008; Stanford et al., 2008). Understanding of IC/PBS diagnosis and treatment lead to earlier recognition and appropriate treatment and improved outcomes for women with IC/PBS.

Currently, there are over 180 different therapies identified to treat IC/PBS, both pharmacologic and non-pharmacologic. However, a gold standard for managing IC/PBS is lacking. Hanno et al. (2011) published the only guideline for the diagnosis and management of IC/PBS. In their guideline, the authors recognized the limitations in the

available literature including poorly defined patient groups, small sample sizes, lack of placebo controls in many studies, the likely over-estimation of efficacy, short follow-up durations, and inconsistency with outcome measure used. These limitations created difficulties in using RCTs for a single meta analysis (Hanno et al., 2011). Hanno et al. (2011) made treatment recommendations based on evidence grades B and C, indicating that there was weakness in the evidence. Current treatment of IC/PBS was aimed at reducing symptoms to a level acceptable for the individual patient and management must be tailored to the individual (Forrest & Moldwin, 2008; Hanno et al., 2011). Options included oral medications, intravascular medications, and behavioral interventions including dietary modification and physical therapy (Forrest & Moldwin, 2008). Most researchers and experts agreed that a multimodal approach to treating IC/PBS combining pharmacologic and non-pharmacologic management strategies, starting with least invasive therapies, yielded the best results for women with IC/PBS (Burrell & Hurm, 1999; Dell, 2007; Dell & Butrick, 2006; Forrest & Moldwin, 2008; Hanno et al., 2011; Klutke & Klutke, 2008).

Pharmacologic interventions.

Elmiron or pentosan polysulfate (PPS) was the only Food and Drug Administration (FDA) approved medication for the treatment of IC/PBS (Hanno et al., 2011; Jamison et al., 2007; Klutke & Klutke, 2008; Rosamilia, 2005; Stanford et al., 2008). The mechanism of action of PPS was not entirely clear, it is believed that it replaces the surface of the GAG layer of the bladder lining and inhibits histamine release by the mast cells, decreasing bladder irritation and pain (Klutke & Klutke, 2008; Rosamilia, 2005).

Other oral medications that are commonly used “off-label” to treat symptoms of IC/PBS included; amitriptyline, antihistamines specifically hydroxazine and cimetidine, benzodiazapines and other muscle relaxants, gabapentin, steroids, anticholinergic medications, non-steroidal anti-inflammatory drugs (NSAIDs), and narcotic and non-narcotic pain relievers (Burrell & Hurm, 1999; Hanno et al., 2011; Jamison et al., 2007; Stanford et al., 2008). The intravesical instillation of dimethyl sulfoxide (DMSO) was also FDA approved for the treatment of IC/PBS; standard treatment with DMSO was considered six doses over a three-month period (Onwude, 2009; Stanford et al., 2008). However, DMSO instillations must be done in a clinic setting by a trained professional and the effect on symptom relief for IC/PBS patients was not certain (Onwude, 2009).

Behavioral interventions.

Several non-pharmacological treatments were recommended for the treatment of symptoms related to IC/PBS. One of the most common was diet modification, many women with IC/PBS reported that symptoms are exacerbated by certain foods it is unclear why certain foods seem to worsen symptoms (Dell & Butrick, 2006; Rosamilia, 2005; Shorter, 2006; Warren, 2007). Foods that women commonly cited as exacerbating IC/PBS symptoms include acidic foods, foods high in potassium, citrus, chocolate, caffeine, spices, alcohol, carbonation, tomatoes, vinegar, and artificial sweeteners (Dell & Butrick, 2006; Rosamilia, 2005; Shorter, 2006). Not all foods in this list exacerbated symptoms in all women with IC/PBS. Recommendations included that women first eliminate all foods and gradually add them back into their diet one at a time to identify offensive foods (Warren, 2007). Other non-pharmacological therapies

that were shown to improve symptoms of IC/PBS include stress management, exercise, smoking cessation, relaxation techniques, pelvic floor exercises and physical therapy, local hot and cold compresses, bladder training, biofeedback, participation in support groups, development of coping skills and maintaining social connections (Dell, 2007; Dell & Butrick, 2006; Forrest & Mishell, 2009; Hanno et al., 2011; Klutke & Klutke, 2008; Rosamilia, 2005; Warren, 2007; Webster & Brennan, 1998).

PICO Question

An extensive review and analysis of literature published from 2002 through 2012 was conducted to answer the following PICOT question: In women ages 18 and older with a diagnosis of IC/PBS, who are not pregnant (P), how do oral pharmacological interventions (I) compare with behavioral interventions (C) best practice for managing IC/PBS in adult women ages 18 and older, evidenced by a decrease in IC/PBS symptoms indicated by a reduction in the patient's ICSI and ICPI scores from baseline or patient self reported improvement of symptoms (T) upon diagnosis? The following table depicts that evidence-based practice question in PICOT format.

Table 1.1: Evidence Based Practice Clinical Question

| Patient Population | Intervention | Comparison Intervention | Outcome | Time |
|--|------------------------------------|--------------------------|---|----------------|
| Adult women ages 18 and older with a diagnosis of IC/PBS, who are not pregnant | Oral pharmacological interventions | Behavioral interventions | Best practice for managing IC/PBS in adult women ages 18 and older, evidenced by a decrease in IC/PBS symptoms indicated by a reduction in the patient's ICSI and ICPI scores from baseline or patient self reported improvement of symptoms. | Upon diagnosis |

PICO Definitions and Descriptions

1. Adult women: any female over the age of eighteen.
2. Behavioral interventions: Modifications that a woman makes to her routine to minimize symptoms of IC/PBS including but not limited to diet modification, stress reduction, physical therapy, biofeedback and exercises targeted at symptom improvement (Dell, 2007; Dell & Butrick, 2006; Forrest & Mishell, 2009; Hanno et al., 2011; Klutke & Klutke, 2008; Rosamilia, 2005; Warren, 2007; Webster & Brennan, 1998).
3. Best practice: The use of interventions and techniques that are grounded in research and known to promote high quality care and patient outcomes (Iowa, 2012).

4. Diagnosis: the use of scientific or clinical methods to establish the cause and nature of a person's illness and functional impairment caused by the pathology (Venes, 2005).
5. Healthcare Provider: refers to advanced practice registered nurses (APRNs), physician's assistants (PA), and physicians that manage the care of women in an outpatient setting.
6. Interstitial Cystitis/Painful Bladder Syndrome: as defined by the Society for Urodynamics and Female Urology defines IC/PBS- an unpleasant sensation, described as pain pressure or discomfort perceived to be related to the urinary bladder and associated with lower urinary tract symptoms of more than six weeks duration in the absence of infection or other identifiable cause (Hanno et al., 2011).
7. O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI): a self-administered one-page assessment of the impact of symptoms of IC/PBS on patient's QOL. Scored from 0 to 36, a score of 36 representing the most severe symptoms. Useful in the evaluation of effectiveness of treatments for IC/PBS (O'Leary et al., 1998; Theoharides, 2007).
8. O'Leary-Sant Interstitial Cystitis Problem Index (ICPI): a self-administered one-page questionnaire designed to assess how problematic IC/PBS is for a patient. Scored from 0 to 36, a score of 36 representing the most severe symptoms. Useful in the evaluation of effectiveness of treatments for IC/PBS (O'Leary et al., 1998; Theoharides, 2007).

9. Patient self-reported symptom reduction: a patient's response to a particular treatment evaluated with an questionnaire that has been developed by researchers to evaluate overall improvement in IC/PBS (Anderson & Perry, 2006; Sairanen et al., 2005).
10. Symptom Reduction: A decrease in disuria, urinary frequency and urgency, pelvic pain and other symptoms associated with IC/PBS, indicated by a 30% reduction in ICSI score from baseline after initiation of treatment (Sand et al., 2008).
11. Pelvic Pain and Urgency/Frequency (PUF) questionnaire: a screening tool validated for identifying patients in a clinical setting with IC/PBS. A score of twelve or higher is indicative of IC/PBS (Forrest & Mishell, 2009; Rosenberg, Page, & Hazzard, 2007).
12. Pharmacological Interventions: Treatment of IC/PBS symptoms with oral or intravesical medication. Including those FDA approved for treatment of IC/PBS and those that have been studied for off label use for treatment IC/PBS (Dell & Butrick, 2006; Hanno et al., 2011).
13. Symptoms of IC/PBS: urinary urgency, frequency, bladder pain, chronic pelvic pain, bladder pain, nocturia, dysuria and dyspareunia (Chaiken et al., 1993; Dell, 2007; Hanno et al., 2011; Heck, 2007).

Summary

IC/PBS is a chronic health condition that predominantly affects adult women. Though the exact prevalence of the disorder is unknown, it was found to affect a significant portion of the population (Forrest & Moldwin, 2008; Ibrahim et al., 2007;

Rosenberg & Hazzard, 2005). IC/PBS was difficult to diagnose and treat because of its variable symptom presentation, a lack of universally accepted diagnostic criteria, and unfamiliarity with IC/PBS by health care providers (Forrest & Mishell, 2009; Klutke & Klutke, 2008; Patel et al., 2008). The abundance of treatment options and a lack of standardized treatment guidelines make determining the best course of treatment challenging for healthcare providers.

The purposes of this project was to 1) conduct a substantive literature review on treatment guidelines for IC/PBS, 2) analyze the literature for comparing oral pharmacological interventions and behavioral interventions for IC/PBS, and 3) determine the best practice recommendation for the reduction of IC/PBS symptoms in women, ages 18 and older.

CHAPTER 2

ANALYSIS OF THE LITERATURE

Introduction

The purposes of this project was to: 1) conduct a substantive literature review on treatment guidelines for IC/PBS, 2) analyze the literature for comparing oral pharmacological interventions and behavioral interventions for IC/PBS, and 3) determine the best practice recommendation for the management of ICS/PBS in adult women, ages 18 and older. Chapter 2 provides an overview of the database findings, a review of the literature available on oral pharmacological interventions for IC/PBS and behavioral interventions for IC/PBS, and an overview of the American Urological Association (AUA) Guideline on diagnosis and treatment of IC/PBS.

Overview

An extensive search of current literature was conducted to answer the PICO question; “in adult women ages 18 and older with a diagnosis of IC/PBS who are not pregnant, how do oral pharmacological interventions compare with behavioral interventions as best practice for managing IC/PBS in women over 18 upon diagnosis?” Initially a search was conducted for pre-appraised synthesized resources through databases such as the Cochrane database of systematic reviews, the Joanna Briggs institute, the National Guideline Clearing House and Annual Reviews (Melnyk & Fineout-

Overholt, 2011; Sairanen et al., 2009; Sairanen et al., 2005)). Unfortunately, a search of these databases yielded few useful results. One guideline on the diagnosis and treatment of IC/PBS published by the American Urological Association Education and Research Inc. was found. The majority of research completed on IC/PBS was in the form of peer-reviewed journal articles and research studies.

The search was broadened to include a thorough search of available bibliographic databases (Melnyk and Fineout-Overholt, 2011). Bibliographic databases searched were CINAHL, Medline (OVID), PubMed-Medline, Web of Science, CSA, Health Source: Nursing/Academic edition, Nursing Resource Center, Essential Evidence Plus, Dissertations and Theses, and Annual Reviews (Melnyk & Fineout-Overholt, 2011). A summary of the search results is provided in table 2.1.

In conducting the search of the literature the following search terms were used, “interstitial cystitis”, “interstitial cystitis and management”, “interstitial cystitis and management and adult women”, “interstitial cystitis and oral management”, interstitial cystitis and behavior management”, “interstitial cystitis and treatment”, “interstitial cystitis and treatment and adult women”, “interstitial cystitis and oral treatment”, “interstitial cystitis and behavior treatment”. Searches included searches of titles, keywords, and abstracts.

Table 2.1 Database Findings

| Database | Key Words | Results |
|-----------------------------------|--|---------|
| Cochrane Library | Interstitial cystitis | 3 |
| | Interstitial cystitis and management | 1 |
| | Interstitial cystitis and oral management | 1 |
| | Interstitial cystitis and behavior management | 0 |
| | Interstitial cystitis and management and adult women | 1 |
| | Interstitial cystitis and treatment | 2 |
| | Interstitial cystitis and oral treatment | 2 |
| | Interstitial cystitis and behavior treatment | 0 |
| | Interstitial cystitis and treatment and adult women | 1 |
| | | |
| Joanna Briggs Institute | Interstitial cystitis | 0 |
| National Guideline Clearing House | Interstitial cystitis | 9 |
| | Interstitial cystitis and management | 8 |
| | Interstitial cystitis and oral management | 6 |
| | Interstitial cystitis and behavior management | 3 |
| | Interstitial cystitis and management and adult women | 6 |

| | | |
|--|---|---|
| | Interstitial cystitis and treatment | 9 |
| | Interstitial cystitis and oral treatment | 6 |
| | Interstitial cystitis and behavior treatment | 3 |
| | Interstitial cystitis and treatment and adult women | 6 |

| | | |
|----------------------------|--|------|
| CINHAL Plus with Full Text | Interstitial cystitis | 443 |
| | Interstitial cystitis and management | 46 |
| | Interstitial cystitis and oral management | 1 |
| | Interstitial cystitis and behavior management | 1 |
| | Interstitial cystitis and management and adult women | 0 |
| | Interstitial cystitis and treatment | 126 |
| | Interstitial cystitis and oral treatment | 5 |
| | Interstitial cystitis and behavior treatment | 0 |
| | Interstitial cystitis and treatment and adult women | 1 |
| | | |
| Medline (OVID) | Interstitial cystitis | 5294 |
| | Interstitial cystitis and management | 1270 |
| | Interstitial cystitis and oral management | 0 |

| | | |
|---------------------------------|--|------|
| | Interstitial cystitis and behavior management | 2 |
| | Interstitial cystitis and management and adult women | 47 |
| | | 3306 |
| | Interstitial cystitis and treatment | 888 |
| | Interstitial cystitis and oral treatment | 281 |
| | Interstitial cystitis and behavior treatment | 68 |
| | Interstitial cystitis and treatment and adult women | 16 |
| | Interstitial cystitis and adult women and behavior treatment | 35 |
| | Interstitial cystitis and oral treatment and adult women | |
| PubMed-Medline (with USC links) | Interstitial cystitis | 2427 |
| | Interstitial cystitis and management | 251 |
| | Interstitial cystitis and oral management | 34 |
| | Interstitial cystitis and behavior management | 16 |
| | Interstitial cystitis and management and adult women | 47 |
| | | 1551 |
| | Interstitial cystitis and treatment | 156 |
| | Interstitial cystitis and oral treatment | |

| | | |
|--|--|------|
| | Interstitial cystitis and oral treatment and adult women | 21 |
| | Interstitial cystitis and behavior treatment and adult women | 15 |
| | Interstitial cystitis and behavior treatment | 66 |
| | Interstitial cystitis and treatment and adult women | 192 |
| Web of Science | Interstitial cystitis | 1985 |
| | Interstitial cystitis and management | 0 |
| | Interstitial cystitis and treatment | 741 |
| | Interstitial cystitis and oral treatment | 66 |
| | Interstitial cystitis and behavior treatment | 17 |
| | Interstitial cystitis and treatment and adult women | 15 |
| Health Source: Nursing/Academic Edition | Interstitial cystitis | 219 |
| | Interstitial cystitis and management | 35 |
| | Interstitial cystitis and oral management | 0 |
| | Interstitial cystitis and behavior management | 0 |
| | Interstitial cystitis and management and adult women | 0 |
| | Interstitial cystitis and | 99 |

| | | |
|--------------------------|--|-----|
| | treatment | 4 |
| | Interstitial cystitis and oral treatment | 4 |
| | Interstitial cystitis and behavior treatment | 0 |
| | Interstitial cystitis and treatment and adult women | |
| Nursing Resource Center | Interstitial cystitis | 2 |
| Essential Evidence Plus | Interstitial cystitis | 29 |
| | Interstitial cystitis and management | 16 |
| | Interstitial cystitis and oral management | 11 |
| | Interstitial cystitis and behavior management | 8 |
| | Interstitial cystitis and management and adult women | 5 |
| | Interstitial cystitis and treatment | 25 |
| | Interstitial cystitis and oral treatment | 13 |
| | Interstitial cystitis and behavior treatment | 8 |
| | Interstitial cystitis and treatment and adult women | 7 |
| Dissertations and Theses | Interstitial cystitis | 287 |
| | Interstitial cystitis and management | 208 |
| | Interstitial cystitis and oral management | 127 |
| | Interstitial cystitis and behavior management | 156 |

| | | |
|----------------|--|-----|
| | Interstitial cystitis and management and adult women | 153 |
| | Interstitial cystitis and treatment | 276 |
| | Interstitial cystitis and oral treatment | 160 |
| | Interstitial cystitis and behavior treatment | 195 |
| | Interstitial cystitis and treatment and adult women | 178 |
| Annual Reviews | Interstitial cystitis | 22 |
| | Interstitial cystitis and management | 10 |
| | Interstitial cystitis and oral management | 5 |
| | Interstitial cystitis and behavior management | 4 |
| | Interstitial cystitis and management and adult women | 0 |
| | Interstitial cystitis and treatment | 5 |
| | Interstitial cystitis and oral treatment | 0 |
| | Interstitial cystitis and behavior treatment | 0 |
| | Interstitial cystitis and treatment and adult women | 0 |

Articles were included if they were published after 2002 to ensure that recent literature and a sufficient quantity of quality studies was used to answer the PICOT question; with the exception of one study that is the foundation of behavioral interventions for IC/PBS. All articles included in this review were limited to those published in English; however, articles from countries other than the United States were included as long as they were available in English. Articles were limited to those that addressed the care of adults, as the population that the PICOT question sought to address was adult women. Articles that exclusively pertained to IC/PBS in men were excluded because the PICOT question specifically addresses the management of IC/PBS in women. However, studies that included both men and women could not be excluded, as some of the findings from these studies are pertinent to the management of IC/PBS in women. Twenty-seven articles were included in this analysis, a summary of each of these articles can be found in the table in Appendix A.

Appraisal of the Evidence

The first priority in selecting articles was to choose articles with a high grade of evidence and whose content most specifically addressed the PICOT question. When choosing which articles to evaluate the hierarchy of evidence that was used to select articles for inclusion and to evaluate those articles was the levels of evidence presented by the Scottish Intercollegiate Guidelines Network (2011) in the guide *SIGN 50*, a reproduction of this hierarchy for grading evidence is included in Appendix B. The SIGN guide has 8 grades of evidence. Grades are as follows from lowest level of evidence to highest: 4 expert opinions, non-systematic reviews of literature and clinical articles; 3

non-analytical studies; 2- case control or cohort studies with high risk of bias; 2+ well conducted case control or cohort studies with low risk of bias; 2++ high quality systematic reviews of case control or cohort studies; 1- meta-analysis, systematic reviews, or randomized control trials (RCTs) with high risk of bias; 1+ well conducted meta analysis, systematic reviews or RCTs with low risk of bias; 1++ high quality meta analysis, systematic reviews of RCTs or RCTs with very low risk of bias (SIGN, 2011). The grade assigned to each piece of evidence is listed in the second column of the table in Appendix A.

The American Urological Association (AUA) Guidelines for the Diagnosis of and Treatment of Interstitial Cystitis/Bladder Pain Syndrome by Hanno et al. (2011) was analyzed as part of this review. The Appraisal of Guidelines Research and Evaluation (AGREE) instrument was used in the analysis of this guideline. The AGREE instrument was used following these instructions, (AGREE, 2011) written by the AGREE Collaboration published in their 2001 guide. Utilizing this instrument this author rated the guideline on its performance in the following six categories: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence (AGREE Collaboration, 2001). Overall the AUA guideline received a 71%, details of the scoring in each categories are listed in the table in Appendix A. The major weaknesses of this guideline are inherent to the lack of available scientific research to support the guideline and the disease process of IC/PBS. The medical community wrote the guideline for patients and healthcare providers based on anecdotal evidence from experts caring for patients with IC/PBS. The authors also did

not address the cost of treatments or consider input from patients with IC/PBS. There is also no plan for how the guidelines will be updated as new research becomes available (Hanno et al. 2011).

Oral Pharmacological Interventions

Twelve articles addressed the use of oral pharmacological interventions for the management of IC/PBS in adult women. Seven of these articles reviewed the use of pentosan polysulfate (PPS) or Elmiron; the other five articles examined the use of other oral medications to manage symptoms of IC/PBS including amitriptyline, anticholinergics, oral contraceptives, muscle relaxants, and antihistamines.

Pentosan polysulfate.

Pentosan polysulfate (PPS) is a semi-synthetic sulfated polysaccharide that is chemically similar to heparin, it was the only oral medication approved by the FDA for treatment of IC/PBS (Anderson & Perry, 2006). The exact pharmacokinetics were not understood well. However, it was documented that PPS repairs the glycosaminoglycan (GAG) layer of the bladder epithelium reducing permeability to toxins (Anderson & Perry, 2006). Eight articles that examined the use of PPS for management of IC/PBS were reviewed; the majority demonstrated the highest levels of evidence (rated 1+ by the SIGN guide) available on the management of IC/PBS.

Nickel et al. (2005) conducted a RCT on the uses of PPS for the management of adults with IC/PBS. In a double-blind analysis of 380 adult women with IC/PBS, Nickel et al. (2005) examined the effect of three dosages of PPS, 300mg daily, 600 mg daily, and 900mg daily. Results showed no statistically significant differences in the responses

among the three treatment groups for dosage, but 17 to 23 percent of participants reported relief after four weeks on PPS therapy. At the end of the thirty-two week study, another 59 to 67 percent of the participants had statistically significant improvement in IC/PBS symptoms even if they did not have improvement at the four-week measurement, regardless of the dose of PPS ($p < .05$) (Nickel et al., 2005). A significant limitation of this study is that there was not a placebo comparison group; all participants were in a treatment group that received PPS in varying doses (Nickel et al., 2005).

A RCT conducted by Sairanen et al. (2005) compared treatment of IC/PBS symptoms with PPS and oral Cyclosporine A. This trial found that Cyclosporine A was significantly more effective ($p < 0.001$) at reducing micturition frequency by fifty percent than PPS after 6 months of treatment (Sairanen et al., 2005). However, adverse events were more common in the Cyclosporine A treatment group; 30 out of 94 patients experienced adverse events including increased blood pressure and increased serum creatinine. Adverse events with PPS were less common and less severe; the most common adverse events were gastrointestinal upset, fatigue and headache (Sairanen et al., 2005). The authors cautioned that though effective, patients treated with Cyclosporine A for IC/PBS should be monitored closely, including regular monitoring of blood pressure and serum creatinine measurements for renal function (Sairanen et al., 2005).

Sairanen et al. used data from the 2005 study in a subsequent 2009 study to compare the effects of IC/PBS treatments on quality of life. The purpose of this study

was to evaluate the treatment effect on the quality of life (QOL) of patients with IC/PBS. Authors surmised QOL is compromised in these patients due to the nature of the chronic disease. There is not an established specific questionnaire for evaluating QOL in patients with IC/PBS. However, the authors used a 30-item questionnaire developed and validated by Cleary et al. (1995) for evaluation of QOL in patients with prostate carcinoma (Sairanen et al., 2009). This questionnaire was a self-administered questionnaire that evaluated the QOL categories of general health perceptions, pain, emotional well-being, vitality, social functioning, physical capacity, and sexual interest and functioning (Cleary, Morrissey, & Oster, 1995). A sample of 550 patients with metastatic prostate cancer was used to validate this questionnaire. Cleary et al. (1995) found that the estimated reliability coefficient (alpha) for the scales in each country studied ranged from 0.82 to 0.96, with the exception of items concerning sexual interest and functioning (alpha >0.74). Correlations between general health perception and other QOL measures were used to determine construct validity. In all subscales, except sexual interest and functioning, the correlation was greater than 0.30 in the predicted direction (Cleary et al., 1995). Limitations exist in the reliability and validity of this questionnaire when evaluating sexual aspects of QOL. Sairanen et al. (2009) used this questionnaire with the exclusion of a question addressing the issue of erectile dysfunction because 89% of the study population was women. The scores between the QOL categories were compared using the Wilcoxon sum test and a one-way ANOVA was applied to calculate the similarity of baseline characteristics between all treatment arms. There were no documented statistically significant differences in baseline

characteristics between the Cyclosporine A and PPS groups (Sairanen et al., 2009). Both the Cyclosporine A and PPS treatment groups saw improvement in QOL scores.

However, the Cyclosporine A therapy had a statistically significantly higher quality of life response score than PPS therapy ($p < 0.001$). Limitations of this study existed due to unresearched modifications of the QOL instrument and its use in this study. Because a QOL tool for the evaluation of patients with IC/PBS did not exist, the authors use a tool validated for another disease. That this tool has the same reliability and validity for evaluating QOL in patients with IC/PBS cannot be assumed. Another limitation or concern was the use of Cyclosporine A in treatment of IC/PBS. This form of treatment was under review and not FDA approved for the management of IC/PBS. Investigators claimed that further studies need to be conducted to support the findings of this RCT by Sairanen et al. (2009) before recommending the use of Cyclosporine A for management of IC/PBS. This Finnish study concluded that while Cyclosporine A is more effective than PPS, side effects were more common and patients must be monitored more closely when taking Cyclosporin A, than when taking PPS (Sairanen et al., 2005).

In a secondary analysis of the RCT by Nickel et al. (2005), Nickel et al. (2008) determined that initiation of PPS therapy within six months of diagnosis with IC/PBS demonstrated statistically significantly improved patient outcomes as measured by improvement in the IC symptom index (ICSI) and IC problem index (ICPI) compared to patients who did not receive PPS until two years or more after diagnosis. The ICSI and ICPI are each a four question self-administered questionnaire that is scored using a Likert Scale 1-5. The ICSI is designed to capture the most important voiding and pain

symptoms and The ICPI is designed to assess how problematic patients find these symptoms in a clear and concise manner, (O'Leary, 1997). These two indices were initially validated in a study that compared responses from 45 patients diagnosed with IC/PBS and 67 volunteers who denied any voiding symptoms. Demographic characteristics of the two groups were not significantly different, with the exception that control subjects were more likely to have higher levels of education (O'Leary et al., 1997). Internal consistency (Cronbach's alpha) for the ICSI exceeded 0.85, and 0.90 for the ICPI. Test-retest reliability exceeded 0.90 for both indices. Construct validity was measured through correlations with two overall measures of significance of symptoms. All but one of the correlations was statistically significant. The authors concluded that the symptom scores for the controls had very little variance (O'Leary et al., 1997). The ICIS and ICIP used together captured the significance of the problem from the patient's perspective. The indices were not intended to be used as screening tools, rather as an adjunct in the diagnosis and in evaluation of management of patients with IC/PBS (O'Leary et al., 1997). Nickel et al. (2008) performed a retrospective sub-analysis of 128 subjects from the previous RCT who received 300 mg a day of PPS. Subjects were categorized into two groups as receiving early treatment or late treatment. Early treatment was defined as treatment within 6 months of the diagnosis of IC and late treatment was defined as treatment initiation 24 months after diagnosis with IC (Nickel et al., 2008). An ANCOVA covariance model, including a category for time since IC diagnosis to PPS initiation as a factor and baseline score as a covariate, was used to compare ICSI and ICPI scores between the two treatment groups (Nickel et al., 2008).

ICSI mean scores in the early treatment group improved by an average of 3.97 points compared to an improvement of 2.15 points in the late treatment group ($p < 0.05$). ICPI mean scores improved an average 3.94 points in the early treatment group and only 1.77 points in the late treatment group ($p < .01$). Authors concluded that patients with IC/PBS benefit from earlier initiation of PPS therapy (Nickel et al., 2008). Limitations of this study included the use of time from diagnosis to initiation of PPS to evaluate time until initiation of treatment. This may not be representative of the duration of IC/PBS symptoms, since many patients with IC/PBS suffer with symptoms for months to years before diagnosis. Both the early and late treatment groups had moderate to severe IC/PBS symptoms at baseline making it difficult to generalize findings to include patients experiencing mild IC/PBS symptoms. The majority of patients had also received at least one medication for IC/PBS before enrollment in the study. This may have created an unknown bias (Nickel et al., 2008).

Sand et al. (2008) also performed a secondary analysis of the RCT conducted by Nickel et al. (2005). Sand et al. (2008) analyzed a subset of 128 women who received 300mg of PPS a day to determine response to treatment. Women were labeled responders to PPS therapy if a 30% reduction in ICIS score was seen at the end of the 32 week study (Sand et al., 2008). Forty-two percent of women were identified as responders to PPS treatment. However, 70% of women studied reported that they experienced a benefit from PPS therapy, and that relief with PPS was greater than any treatment that they had previously tried (Sand et al., 2008). The majority of subjects (91%) were women, 95% of these women were considered to have moderate to severe

baseline IC symptoms. Using the criteria of a reduction of 30% or more in ICSI scores to define patients as responders, 42% (49 patients) responded to PPS (Sand et al., 2008). PPS treatment responders were statistically significantly more likely to have higher ratings on the treatment satisfaction questionnaire than non-responders ($p < 0.001$). Fisher's exact two sided test and Odds ratio analysis found responders were 6.27 times more likely to be pleased with PPS ($p < 0.001$), 6.17 times more likely to benefit from PPS for IC/PBS symptoms ($p < 0.001$) and 2.73 times more likely to recommend PPS for IC/PBS symptoms ($p < 0.005$) (Sand et al., 2008). Seventy-nine percent of responders reported that PPS provided better relief than previous treatments ($p < 0.005$). Among all subjects, 70% reported a benefit from PPS at the end of the treatment period, even if they were not identified as responders (Sand et al., 2008). The limitations of this study were related to the sample extracted from the original RCT. The sub-sample from the original RCT analyzed in this study was relatively small ($n=128$). The majority of subjects (91%) were women with moderate to severe IC/PBS symptoms at baseline, making it difficult to generalize this data to a population of IC/PBS patients with mild symptoms (Sand et al., 2008).

Dimitrakov et al. (2007) conducted a systematic review of RCTs for pharmacologic treatment of patients with IC/PBS. The authors included 21 RCTs that were published between 1987 and 2006 that met inclusion criteria. Articles were excluded if they did not address treatment of IC/PBS or report global or symptom-specific outcomes, did not use RCT double blind placebo controlled design, include patients without a diagnosis of IC/PBS, were incomplete or duplicate publications, were

not in English, or had a sample size of less than 10 (Dimitrakov et al., 2007). A total of 1470 adults participated in the 21 RCTs; 90% of these were women (Dimitrakov et al., 2007). Global and individual symptom improvement was reported in all of the studies reviewed, global improvement was viewed as the common outcome across all treatments and was usually reported as the number of patients reporting self-improvement in each group (Dimitrakov et al., 2007). The average frequency of global improvement was 19% among control groups and 49% among treatment groups for all RCTs. Only trials for treatment of IC/PBS with PPS had sufficient numbers to allow a pooled analysis of effect using a random-effects model (Dimitrakov et al., 2007). Six RCTs and one meta-analysis addressed treatment with PPS, the pooled analysis by Dimitrakov et al. (2007) suggested a benefit from treatment ($p < .05$).

In a review of research literature on PPS for treatment of IC/PBS, Anderson and Perry (2006) found that PPS had a beneficial effect for a large portion of patients with IC/PBS. Anderson and Perry (2006) conducted a search of medical literature published in any language from 1980 to 2006. Studies were captured if they included patients diagnosed with IC/PBS who received PPS. When available large, well controlled trials with appropriate statistical methodology were preferred, however relevant pharmacodynamic and pharmacokinetic data were also included (Anderson & Perry, 2006). According to Anderson and Perry (2006), the evidence supported the use of PPS for management of IC/PBS. PPS was generally well tolerated, easy to use over invasive medications, and demonstrated statistical significance in reducing pain over time. Research showed that it is a more convenient treatment option than other FDA

approved intravesical medications, such as DMSO that required clinical visits and were time consuming and painful (Anderson & Perry, 2006). They also found that data from non-comparative studies showed that PPS was effective over a 116-month period. Patients should be advised that it may take 3 to 6 months to see full treatment effect, and treatment may need to be continued indefinitely to maintain effect. However, patients who have not seen efficacy of PPS in a treatment period greater than 6 months were not likely to show statistically significant improvement in pain with PPS (Anderson & Perry, 2006). Anderson and Perry (2006) concluded that PPS was beneficial for improvement of overall condition and relief of pain for patients with IC/PBS but that the degree of improvement varied among patients.

Two articles based on expert opinion by Parsons (2002 & 2006) stated that the use of PPS was successful in the treatment of IC/PBS, but duration of treatment was more important than dosage, Parsons also found younger patients 10 to 30 years old had good symptom improvement over a 2 to 4 month period. Parsons (2006) noted that PPS improved symptoms of IC/PBS by correcting the dysfunction of the GAG bladder lining. The author noted that studies did not explore the added benefit of treating IC/PBS with PPS in conjunction with other oral medications (Parsons, 2006). Therefore, Parsons (2006) suggested that optimal management of IC/PBS was through a multimodal approach that included the use of PPS.

Other oral medications.

Other medications used in the management of IC/PBS included antihistamines, tricyclic-antidepressants (TCAs) such as amitriptyline, anticholinergics, and skeletal

muscle relaxants (Dell & Butrick, 2006). Five articles examined the use of oral pharmacological agents other than PPS for the management of IC/PBS.

In their systematic review of 21 RCTs for management of IC/PBS, Dimitrakov et al. (2007) found that amitriptyline is effective therapy of IC/PBS ($p < 0.05$). However, hydroxysine did not show a significant effect on symptom reduction ($p > 0.05$). One RCT on the use of amitriptyline to treat IC/PBS found that 15 of 24 patients had symptomatic relief with an average dose of 75 mg daily. However, the study did not provide details regarding the use of active or inactive placebo between groups ($p < .05$) (Dimitrakov et al., 2007). Many RCTs had short duration study times, did not account for the variability of IC/PBS symptoms over time, had inadequate blinding, small sample sizes (less than 30), or non-standardized evaluation outcomes making the determination of optimal treatment difficult between studies. The authors concluded, based on the limitations in the trials, that other than for PPS, there was insufficient evidence to recommend the use of other pharmacological therapies (Dimitrakov et al., 2007). Moreover, they concluded that thus far, trials for treatment of IC/PBS with PPS had sufficient sample numbers to allow a pooled analysis of effect using a random-effects mode. For the remaining treatment modalities, a pooled analysis was not attempted due to a wide variety of designs and small sample sizes. The authors attempted to abstract data as a standardized mean difference to produce measure of effect for each treatment trial on a similar metric, however it was not possible to classify results as positive or negative outcome in terms of efficacy (Dimitrakov et al., 2007).

A cross-sectional study of 750 patients with IC/PBS investigated the medications pH modulator Prelief, phenazopyridine and PPS use for improved symptoms (Hill, Isom-Batz, Panagopoulos, Zakariasen, & Kavalier, 2008). Hill et al. (2008) surveyed patients via a computer based Internet survey that was linked on the Interstitial Cystitis network, national Women's Health Network and Our Bodies Ourselves websites. Questions included demographic data, and specific information about procedures and medications used to treat IC/PBS and whether patients perceived their condition as improved, not affected, or deteriorated after treatment (Hill et al., 2008). Statistical analyses were conducted (chi-squared tests) to compare the perceptions of each treatment group (three treatment groups) for outcomes: improved, no effect or worse (Hill et al., 2008). Statistically significant improvements were reported among groups for all drugs examined ($p < 0.001$). Of the 52.7% ($n = 395$, $N = 750$) of individuals who were prescribed PPS, 53.4% found that the medication improved IC/PBS symptoms, 3.8% reported worse symptoms, and 29.9% reported no effect. Thirteen percent of patients reported intolerable side effects with PPS ($p < 0.001$) (Hill et al., 2008). Other medications that significantly improved patients' IC/PBS symptoms include phenazopyridine, calcium glycerophosphate (Prelief), amitriptyline, and codeine. Vistaril, tolterodine, oxybutynin, oxybutyninXL, and diphenhydramine were reported to have no effect on IC/PBS symptoms ($p > .05$) (Hill et al., 2008). Patients also found that oral medications were better than invasive therapy for management of IC/PBS symptoms (Hill et al., 2008).

Schmid et al. (2011) conducted a prospective cohort study of women diagnosed with IC/PBS to determine if their treatment algorithm based on current literature affected sexual function, quality of life and symptoms in women with IC/PBS. Seventy-two patients diagnosed with IC/PBS based on the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) criteria completed the study. The NIDDK developed criteria for clinical trials to ensure that patient populations were similar, the criteria were strict, and included changes seen on cystoscopy as a criteria for diagnosis (Hanno, 2002). Figure 2.1 shows the complete list of the NIDDK criteria for the diagnosis of IC/PBS. The treatment algorithm used by Schmid et al. (2011) followed a stepwise approach to the treatment of IC/PBS starting with oral tetracycline, progressing to bladder instillations, and eventually neurostimulation if symptoms did not improve. Quality of life was assessed by the King's Health Questionnaire, a visual analogue scale (VAS) that assessed symptom severity (Schmid et al., 2011). The King's Health Questionnaire was a questionnaire that determined various aspects of quality of life such as sleep, symptom bother, physical limitations, role limitations and emotions. This 21 question self-administered questionnaire was designed and validated to assess condition-specific quality of life of women with urinary incontinence (Kelleher, Cardozo, Khullar, & Salvatore, 1997). The questionnaire was administered to 293 women prior to the date of a scheduled urodynamic study, to evaluate reliability. The women were then asked to complete the questionnaire again after the completion of these studies. Cronbach's alpha was greater than 0.7 in all domains of the questionnaire (Kelleher et al., 1997). One hundred and ninety-three women who completed the King's Health

Questionnaire also completed the Short Form 36 questionnaire, which was validated as a tool for measuring quality of life. A statistically significant ($p < 0.01$) correlation existed between scores on the King's Health Question and the Short Form 36 in all domains evaluated by the Short Form 36, some domains on King's Health Questionnaire specifically relating to urinary symptoms are not evaluated by the Short Form 36 (Kelleher et al., 1997). A visual analogue scale (VAS) was used by Schmid et al. (2011) to quantify the severity of symptoms. Women were asked to name their most bothersome symptoms and apply a rating of 0 to 10 using the VAS; 0 being the least bother and 10 the worst possible bother of bladder symptoms. The authors did not elaborate on the reliability and validity findings of the scale when used for evaluating the severity of bladder symptom bother. A two-tailed t test compared mean scores before and after treatment (Schmid et al., 2011). Researchers found that a stepwise approach to management of symptoms with tetracycline, oral steroids, and antihistamines significantly improved sexual function and quality of life in women with IC/PBS. VAS scores for pain improved significantly after receiving treatment ($p < 0.001$), as did nocturia ($p < 0.01$) and urinary frequency ($p < 0.01$) (Schmid et al., 2011). However, urgency was not statistically significantly improved using this treatment algorithm ($p > 0.09$). All domains of the King's Health Questionnaire showed significant improvement ($p < 0.001$) with the exception of incontinence impact ($p > 0.227$) (Schmid et al., 2011). Weaknesses of this study included the use of a VAS that was not clearly defined and not validated for measurement of pain or symptom bother in this patient population. Study results may not be able to be applied to a general IC/PBS population due to the

restrictive nature of the NIDDK diagnostic criteria. In addition, using patients who had histories of failures with other treatments might suggest that these patients may have had more severe symptoms than the general population of IC/PBS patients.

Two reviews of available medical literature examined the use of oral medications for the management of IC/PBS. Unwin (2011), in a review of current evidence for Essential Evidence, concluded that treatment of IC/PBS with PPS, amitriptyline and bladder instillation with DMSO are the cornerstones of treatment. This recommendation was supported by level B evidence indicating that further research is needed and that the evidence is inconsistent or of poor quality (Unwin, 2011). The strongest evidence (level A), well conducted controlled studies, supported the use of amitriptyline for the treatment of pain, urgency and frequency associated with IC/PBS. Amitriptyline was considered safe and effective and best used in conjunction with PPS and non-pharmacologic management such as bladder training, diet, counseling and physical therapy (Unwin, 2011). In an analysis of available literature on the treatment of IC/PBS Onwude (2009) found that there were no standardized treatment recommendations for IC/PBS and that current RCTs offered conflicting results. The author recommended that clinicians and patients understand that evidence on treatment of IC/PBS is limited and that they set realistic goals for management (Onwude, 2009).

Summary.

The most rigorous studies examined the use of PPS for treatment of IC/PBS. Current evidence supported the use of PPS for the treatment of IC/PBS. PPS is the only

medication that is FDA approved for treatment of IC/PBS, and is generally well tolerated (Anderson & Perry, 2006; Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sairanen et al., 2009; Sairanen et al., 2005; Sand et al., 2008). The recommended dose of PPS is 300mg daily divided into three 100mg doses. Nickel et al. (2005) found that longer duration of treatment led to better outcomes. In a subsequent study, Nickel et al. (2009) found that early initiation of treatment also improved patient outcomes. Sand et al. (2008) used data from the RCT conducted by Nickel et al. (2005) and found that in the majority of patients PPS was more effective than other therapies. In a pooled analysis of 6 RCTs, Dimetrakov et al. (2007) found data to support the use of PPS in management of IC/PBS.

Other oral medications assisted with the symptoms of IC/PBS. Sairanen et al. (2005) found that Cyclosporine A was more effective at relieving symptoms of IC/PBS, however the side effects associated with Cyclosporine A were significantly higher than those associated with PPS. Other medications including phenazopyridine, calcium glycerophosphate (Prelief), amitriptyline, and codeine were shown to help relieve symptoms of IC/PBS taken in adjunct with PPS (Hill et al., 2008; Unwin, 2011). While there is lower level evidence that phenazopyridine, Prelief, amitriptyline, and codeine are effective in relieving symptoms of IC/PBS, RCTs are needed to be conducted to demonstrate efficacy, especially for off label use for the management of IC/PBS.

| The National Institute of Diabetes and Digestive and Kidney Diseases Consensus Criteria for the Diagnosis of Interstitial Cystitis | |
|---|-----------------------------|
| To be diagnosed with interstitial cystitis, patients must have either: | |
| Glomerulations on cystoscopic examination | Or a classic Hunner's ulcer |
| and either: | |
| Pain associated with the bladder | Or urinary urgency |
| An examination for glomerulations should be undertaken after distention of the bladder under anesthesia to 80–100 cm of water pressure for 1–2 minutes. The bladder may be distended up to two times before evaluation. | |
| The glomerulations must: | |
| Be diffuse—present in at least 3 quadrants of the bladder | |
| Be present at a rate of at least 10 glomerulations per quadrant | |
| Not be along the path of the cystoscope (to eliminate artifact from contact instrumentation). | |
| The presence of any one of the following criteria excludes the diagnosis of interstitial cystitis: | |
| 1. Bladder capacity of greater than 350 cc on awake cystometry using either a gas or liquid filling medium | |
| 2. Absence of an intense urge to void with the bladder filled to 100 cc of gas or 150 cc of water during cystometry, using a fill rate of 30–100 cc/min | |
| 3. The demonstration of phasic involuntary bladder contractions on cystometry using the fill rate described above | |
| 4. Duration of symptoms less than 9 months | |
| 5. Absence of nocturia | |
| 6. Symptoms relieved by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics | |
| 7. A frequency of urination, while awake, of less than 8 times per day | |
| 8. A diagnosis of bacterial cystitis or prostatitis within a 3-month period | |
| 9. Bladder or ureteral calculi | |
| 10. Active genital herpes | |
| 11. Uterine, cervical, vaginal, or urethral cancer | |
| 12. Urethral diverticulum | |
| 13. Cyclophosphamide or any type of chemical cystitis | |
| 14. Tuberculous cystitis | |
| 15. Radiation cystitis | |
| 16. Benign or malignant bladder tumors | |
| 17. Vaginitis | |
| 18. Age less than 18 years | |

Figure 2.1: NIDDK Diagnostic Criteria from Hanno (2002)

Behavioral Interventions

A dearth of literature exists examining the effectiveness of behavioral interventions beyond case reports, anecdotal reports, and expert opinions. Chaiken, Blaivas, and Blaivas (1993) conducted a case study of 42 women with persistent symptoms of urinary frequency and pain that increased in intensity when voiding was delayed and was produced by bladder filling (Chaiken et al., 1993). This study examined the effect of behavioral therapy on urgency, frequency and pain related to IC/PBS. All of the women in this study had tried other treatments for IC/PBS including antibiotics, tricyclic antidepressants, muscle relaxers, anticholinergics, sedatives, intravesical instillations and mechanical interventions such as urethral dilation and hydrodistention. Patients noted temporary improvement from these therapies but no long-term relief

(Chaiken et al., 1993). In their study, participants attended one 45-minute behavioral therapy session per week for 8 to 12 weeks. An experienced therapist with training in psychology and lower urinary tract physiology performed therapy (Chaiken et al., 1993). Baseline values for total daytime void volumes, maximum voided volume, mean voided volume, maximum and mean inter-voiding intervals and total number of micturitions was recorded. Post treatment values in the same categories were determined and patients were asked to rate their global results of therapy as markedly improved, improved, unimproved or worse. Baseline and post treatment mean values for void volumes, maximum voided volume, mean voided volume, maximum and mean inter-voiding intervals, and total number of micturitions were compared using a t-test (Chaiken et al., 1993). Over half of the women who participated reported that their symptoms were improved and the average increase in interval between voids was 123 minutes (Chaiken et al., 1993). The functional bladder capacity increased in 38 of 42 patients ($p < 0.01$), inter-voiding interval increased in all patients by an average of 93 minutes ($p < 0.01$), the maximum interval increased in 38 of 42 patients ($p < 0.01$) and 41 patients experienced a decrease in the number of micturitions a day by an average of 9 ($p < 0.01$) (Chaiken et al., 1993). The authors concluded that behavioral therapy was effective in reducing symptoms associated with IC/PBS. However, therapy required a highly motivated patient and access to a skilled therapist in order to be successful (Chaiken et al., 1993). This study was the most rigorous scientific study to date evaluating the effect of behavior modification of symptoms of IC/PBS. This rigor justified its inclusion for this review, despite the date of publication.

Chaiken et al. (1993) studied women who had failed treatment of IC/PBS with antibiotics, tricyclic antidepressants, muscle relaxers, anticholinergics, sedatives, intravesical instillations and mechanical interventions such as urethral dilation and hydrodistention. Some of these treatments are still used for IC/PBS. However since the publication of Chaiken et al.'s study, new treatments have become available, such as PPS. Currently, there have not been well-controlled trials comparing behavioral modification such as those examined by Chaiken et al. (1993) to current pharmacological therapy available for IC/PBS, such as PPS. An additional weakness was that results from this study were not able to be generalized to all women with IC/PBS. Women included in this study completed a detailed voiding journal; 16 participants were excluded from the results because of a failure to keep the voiding journal. Behavioral therapy requires highly motivated patients and skilled therapist. Women included in this study were motivated to meet all participation requirements, yet future IC/PBS patients may not have the motivation or resources to successfully complete behavioral therapy.

Researchers identified stress reduction as an important component of management of IC/PBS. Increased stress levels appeared to exacerbate IC/PBS symptoms (Hanno et al., 2011; Rosamilia, 2005; Rosenberg, Newman, et al., 2007; Rothrock et al., 2003). A case report of 64 women with diagnosed IC/PBS, meeting the NIDDK definition of IC/PBS, sought care at a participating clinic. They completed questionnaires and a standardized semi-structured depression interview at scheduled clinic appointments (Rothrock et al., 2003). Participants completed the Beck Depression

Inventory, the Hamilton Rating Scale for Depression, and the Medical Outcome Study. Regression models were constructed to test the relationships among coping strategies, quality of life and depression. The Beck Depression Inventory (BDI), a 21-item instrument that assessed the severity of depressive symptoms on a Likert scale, had reliability and validity demonstrated in populations with chronic illness (Rothrock et al., 2003). The BDI was studied over a 25 year period with psychiatric and non-psychiatric samples. A meta-analysis of the BDI's internal consistency estimated an alpha coefficient of 0.86 for psychiatric patients and 0.81 for non-psychiatric patients (Beck, Steer, & Carbin, 1988). Correlations between the BDI samples with clinical ratings were high, 0.72 for psychiatric patients, and 0.60 for non-psychiatric patients. Correlations between the BDI and the Hamilton Psychiatric Rating Scale for Depression were also high, 0.73 for psychiatric patients and 0.74 for non-psychiatric patients. These results indicated that the BDI reliably differentiates depression from anxiety and is reliable for use across populations (Beck et al., 1988). The Hamilton Rating Scale for Depression (HRSD) is a 21 item structured interview that assessed depressive symptoms over the last week. Depressive symptoms are rated on a 0 to 2 or 0 to 4 scale for severity the higher score indicated greater depressive symptoms (Rothrock et al., 2003). Correlations between the BDI and HRSD were statistically significant ($p < 0.001$, $r = 0.45$) (Rothrock et al., 2003). The Medical Outcomes Study 36-Item Short Form (MOS) assessed 8 areas of functioning: physical function, role-physical, role-emotional, bodily pain, general health, vitality, social functioning, and mental health. A higher score indicated a better quality of life (Rothrock et al., 2003). The MOS was validated by

creating four groups of patients based on clinical criteria differing in severity of medical and psychiatric conditions. Comparisons among these four clinical groups tested the validity of the scales in detecting decrements in health status associated with chronic medical and/or psychiatric conditions (McHorney, Ware, & Raczek, 1993). Scores between the four patient groups were statistically significantly different ($p < 0.01$) in all 8 scales. Patients with serious medical conditions scored significantly lower ($p < 0.01$) on all scales compared to patients with minor medical conditions (McHorney et al., 1993). Rothrock et al. (2003) used age and symptom severity as covariates in these models. Researchers found that age and symptom severity were not associated with depressive symptoms or mental health. However, greater severity of symptoms were associated with catastrophizing (HPRSD) ($p < 0.05$) and venting ($p < 0.01$) (Beck Depression Inventory) (Rothrock et al., 2003). Seeking instrumental support was associated with a decrease in depressive symptoms ($p < 0.01$). Younger age ($p < 0.05$) and increased symptoms severity ($p < 0.001$) were significantly associated with increased pain (Rothrock et al., 2003). Maladaptive coping strategies were associated with higher levels of depressive symptoms and decreased quality of life in patients with IC/PBS (Rothrock et al., 2003). Authors concluded that psychosocial interventions aimed at increasing adaptive coping improved symptoms and quality of life for women with IC/PBS (Rothrock et al., 2003).

Shorter (2006) in a case study and non-systematic review of literature found that anecdotal data gathered from patients and experts demonstrated that eliminating certain foods from the diet may decrease pain associated with IC/PBS in most patients.

Foods commonly found to exacerbate symptoms included alcoholic beverages, coffee, tea, carbonated beverages, tomatoes and certain spices (Shorter, 2006). Foods that exacerbated symptoms for one woman did not exacerbate symptoms for another woman with IC/PBS. Additionally, caution is warranted not eliminate too many foods as that may result in a deficiency of essential nutrients (Shorter, 2006). Tettamani et al. (2001) conducted a case control twin study examining the effects of smoking, tea and coffee consumption on IC/PBS symptoms. The authors found that tea consumption and smoking were positively associated with symptoms of IC/PBS ($p < .05$); but coffee consumption was not associated with symptoms of IC/PBS. The association of smoking to IC/PBS symptoms may be confounded by genetic factors (Tettamanti et al., 2011). Disease and exposure were measured at the same time in this study; therefore, conclusions about whether the exposure preceded or resulted from the disease were not made.

Summary.

Strong scientific evidence for the support of using behavior modification for the treatment of IC/PBS is lacking. A few studies showed that there were some benefits to stress reduction, behavior modifications, improved coping mechanisms, and diet modifications (Chaiken et al., 1993; Rothrock et al., 2003; Tettamanti et al., 2011). Most experts agreed that there was not enough evidence to support the use of behavior modifications alone to manage IC/PBS (Dell & Butrick, 2006; Hanno et al., 2011; Theoharides, 2007; Unwin, 2011).

Multimodal therapy

The majority of experts agreed that the best approach to management of IC/PBS was through a combination on medications and behavioral therapy. Scientific studies on the treatment of IC/PBS yielded mixed results as to the effectiveness of pharmacological treatment versus behavioral management of IC/PBS symptoms. Rather, urologists and other experts in management of IC/PBS recommended a multimodal approach to therapy tailored to the individual.

Most of the evidence on multi-modal management was derived from expert opinions. Experts indicated that management of symptoms focused on attaining an acceptable quality of life for women with IC/PBS by treatment of the dysfunctional bladder epithelium, associated allergies and neural upregulation (Dell & Butrick, 2006; Quillin & Erickson, 2012). They recommended that oral medications as second line therapy or adjunct to enhance behavioral modifications (Dell & Butrick, 2006; Forrest & Moldwin, 2008; Quillin & Erickson, 2012). Recommended oral medications included PPS, antihistamines such as hydroxysine, and cimetidine, TCAs like amitriptyline, analgesics, and skeletal muscle relaxants (Dell & Butrick, 2006; Forrest & Dell, 2007; Forrest & Mishell, 2009; Forrest & Moldwin, 2008; Rosamilia, 2005; Rosenberg, Newman, et al., 2007). Experts recommended management of IC/PBS should begin with the most conservative treatments, including diet modification by eliminating high potassium and acidic foods, stress reduction, exercise, bladder training, biofeedback, and pelvic floor muscle physical therapy if appropriate (Dell, 2007; Dell & Butrick, 2006; Forrest & Dell,

2007; Forrest & Mishell, 2009; Forrest & Moldwin, 2008; Rosamilia, 2005; Rosenberg, Newman, et al., 2007).

Summary.

Current research lacked studies on the effectiveness of a multimodal approach to treatment of IC/PBS. Experts agreed that due to inconsistent results in control trials and studies of pharmacological and behavior management of IC/PBS symptoms, the best approach to management of IC/PBS is a combination of treatments tailored for each patient (Dell, 2007; Dell & Butrick, 2006; Forrest & Dell, 2007; Forrest & Moldwin, 2008; Theoharides, 2007). Patient education was a key part of management of IC/PBS. Patients should understand a) that the etiology of IC/PBS is not fully understood and b) that IC/PBS is a chronic condition for which there is currently no cure. The goal of treatment of IC/PBS is not complete elimination of symptoms, but to achieve a quality of life that is acceptable for the patient (Dell & Butrick, 2006; Forrest & Moldwin, 2008; Quillin & Erickson, 2012).

Guideline for Management of IC/PBS

Hanno et al. (2011) published the only guideline for IC/PBS. The American Urological Association Guideline for the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome (AUA Guideline) is a guideline that provides direction to clinicians and patients regarding the symptom recognition of IC/PBS, conducting diagnostic procedures, and treatment management.

A committee of urologists, nurses and other clinicians with specific expertise on IC/PBS developed the AUA guideline. The committee conducted a systematic review of

published articles relevant to the diagnosis and treatment of IC/PBS. Studies included those published in English between 1983 and 2009 (Hanno et al., 2011). Meta-analysis of randomized controlled trials and systematic reviews were used to analyze the evidence. Bodies of evidence received grades of A, B or C to indicate the strength of the evidence available for particular recommendations. Grade A were well-conducted RCTs or very strong observational studies; grade B consisted of RCTs with some weakness of procedure or generalizability or strong observational studies; observational studies that are inconsistent, have small sample sizes or have other problems that confound interpretation of data were graded level C (Hanno et al., 2011). Due to a lack of high quality evidence on the diagnosis and overall management of IC/PBS, the diagnosis and management portions of the algorithm provided clinical principles or expert opinion (Hanno et al., 2011). The AUA defined a clinical principle as, “a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature” (Hanno et al., 2011, p. 2163). The definition of an expert opinion was, “as a statement that is achieved by consensus of the committee based on members clinical training, experience, knowledge and judgment for which there is no evidence” (Hanno et al., 2011, p. 2163).

The AUA guideline provided an algorithm for diagnosis and treatment, included in Appendix C (Hanno et al., 2011). First line treatments recommended by the AUA guideline as clinical principles included: a) general relaxation and stress management, b) patient education, c) self-care and behavior modification. Self-care and behavior modification included: a) avoiding behaviors that worsen symptoms, b) avoidance of

foods that are known bladder irritants such as citrus, c) pelvic floor muscle relaxation, and d) bladder training (Hanno et al., 2011). The use of the oral medications PPS, amitriptyline, cimetidine and hydroxyzine were second line treatments due to possible minor side effects and unpredictable efficacy for individuals. This recommendation was based on evidence graded levels B and C by the committee (Hanno et al., 2011). The AUA Guideline stated that the use of long-term oral antibiotics is an ineffective treatment that should not be used for IC/PBS. The level of evidence for this statement is grade B and for this reason, it is considered a standard by the AUA. The AUA defined a standard as a directive statement that an action should or should not be undertaken based on Grade A or B evidence (Hanno et al., 2011). The AUA guideline also listed as a recommendation that systemic oral long-term glucocorticoids should not be used to manage IC/PBS (Hanno et al., 2011). The AUA defines a recommendation as, “a directive statement that an action should or should not be undertaken based on Grade C evidence” (Hanno et al., 2011, p. 2163). According to the AUA Guideline, the goal of treatment of IC is to minimize symptoms and adverse events while maximizing the quality of life for patients. No single treatment has been found that is effective for the majority of women with IC/PBS (Hanno et al., 2011).

To appraise the AUA Guideline for quality of evidence, The Appraisal of Guidelines Research and Evaluation (AGREE) instrument was used. The AGREE instrument was designed to appraise the quality of patient care guidelines to determine that the recommendations made are internally and externally valid, as well as feasible for practice (AGREE Collaboration, 2001). The AGREE instrument used 23 items in the six

categories to determine the quality of the recommendations: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence (AGREE Collaboration, 2001). Each of the items was rated on a 4 point scale ranging from 4 strongly agree to 1 strongly disagree. The category score was then determined by standardizing the total as a percentage of the maximum possible score for the category (AGREECollaboration, 2001). Each category score was independent and were not aggregated into a single quality score, a threshold for the category scores to determine if the guideline is “good” or “bad” was not set (AGREECollaboration, 2001). The scores in each category for the AUA guideline were as follows: Scope & purpose 78%, Stakeholder involvement 67%, Rigor 71%, Clarity 92%, Applicability 11%, and Editorial independence 67% (AGREECollaboration, 2001; Hanno et al., 2011). The lowest score for the AUA guideline was in the category of applicability. According to the AGREE Collaboration (2001), a guideline should discuss potential organizational barriers in applying the recommendations, the potential cost of applying recommendations and key review criteria for monitoring and audit purposes to measure adherence to the guideline. The AUA guideline did not address monitoring adherence or provide criteria for audit purposes (Hanno et al., 2011). The AUA guideline did present statistics on the current cost of IC/PBS and the burden on the patient and medical community. The authors did not address how implementation of their recommendations could impact the cost of treatment (Hanno et al., 2011). The intended users of the AUA Guideline are Advanced Practice Nurses, Physician Assistants and Physicians practicing in the areas of family practice, internal medicine, obstetrics

and gynecology, and urology (Hanno et al., 2011). The AUA guideline did not make any recommendations regarding: a) which treatments should be offered in primary care or family practice, b) which would require a referral to a specialist, or c) at what point in management of IC/PBS referral is appropriate (Hanno et al., 2011). Other weaknesses of the AUA guideline for IC/PBS were inherent to the lack of available scientific research to validate recommendations for the treatment of IC/PBS.

Summary

The purposes of this project are to: 1) conduct a substantive literature review on treatment guidelines for IC/PBS, 2) analyze the literature for comparing oral pharmacological interventions and behavioral interventions for IC/PBS, and 3) determine the best practice recommendation for the management of ICS/PBS in adult women, ages 18 and older. Currently many providers are unfamiliar with IC/PBS and the appropriate best practice for managing IC/PBS in women. Women are commonly treated with antibiotics despite negative urine cultures and a lack of response in the past to antibiotic therapies (Clemens et al., 2010). A review of current literature and development of best practice recommendation for management of IC/PBS in women aids health care providers in recognizing IC/PBS early and initiating appropriate treatments, thus decreasing unnecessary and inappropriate treatments and improving the quality of life of women with IC/PBS (Clemens et al., 2010; Patel et al., 2008).

The scientific studies addressing the management of IC/PBS that are available to date focused on the treatment of IC/PBS with pharmacological measures. The strongest evidence in the form of RCTs, meta analysis, cohort studies and case studies focused on

the treatment of IC/PBS with pharmacological medications, primarily PPS (Anderson & Perry, 2006; Dimitrakov et al., 2007; Hill et al., 2008; Nickel et al., 2005; Nickel et al., 2008; Sairanen et al., 2005; Sand et al., 2008). A few case studies reported the potential benefit of behavior modification, diet and stress reduction for the management of IC/PBS, however strong scientific evidence to support these treatments was lacking (Chaiken et al., 1993; Rothrock et al., 2003; Tettamanti et al., 2011). Many experts recommended managing IC/PBS with a multimodal treatment approach (Dell, 2007; Dell & Butrick, 2006; Forrest & Dell, 2007; Forrest & Moldwin, 2008; Hanno et al., 2011; Theoharides, 2007). There were many anecdotal cases reports and expert opinions that supported this multimodal method of treatment. However, strong scientific evidence to show that a multimodal approach achieved the best patient outcomes was lacking.

CHAPTER 3

GUIDELINE

Interstitial Cystitis/Painful Bladder Syndrome is a chronic condition that affects approximately 20 to 25 percent of non-pregnant adult women in the United States (Burkman, 2004; Parsons, 2002). Many providers were unfamiliar with the diagnosis and management of IC/PBS and patients suffering from the disease were undiagnosed or misdiagnosed (Forrest & Moldwin, 2008; Heck, 2007). It was not uncommon for women with IC/PBS to suffer with symptoms for five years or more before they received the correct diagnosis and appropriate management (Heck, 2007). Early diagnosis and management was shown to lead to better patient outcomes, better response to available therapy and increased quality of life (Forrest & Moldwin, 2008; Parsons, 2006). Current research showed that primary care providers are unfamiliar with the diagnosis of IC/PBS and proper management (Clemens et al., 2010). In a survey of primary care physicians, Clemens et al. (2010) found that many of primary care physicians had erroneous beliefs about IC/PBS, including the belief IC/PBS was caused by a psychiatric illness or an STD. Only 67% of the physicians surveyed correctly identified that the hallmark symptom of IC/PBS as bladder pain or pressure (Clemens et al., 2010). Physicians were also unfamiliar with appropriate treatment and diagnostic testing for IC/PBS. Physicians often conducted tests for Chlamydia and gonorrhea, serum

creatinine, cervical cultures, and pelvic ultrasounds and treated patients with NSAIDS, anticholinergics and antibiotics despite negative urine cultures and no response in the past to antibiotic therapies (Clemens et al., 2010). Improving outcomes for women with IC/PBS depends on improving healthcare providers' familiarity with the disease and its management. An evidenced based guideline outlining best practice for the management of IC/PBS would improve outcomes for women with IC/PBS.

Literature Search

The search of current literature included a search of guideline databases to determine what guidelines on the management of IC/PBS existed. A search of the term "interstitial cystitis" in the National Guideline Clearinghouse (NGC) yielded eleven results. However, only one pertained to IC/PBS, the remaining results included chronic pelvic pain, haematuria, incontinence in women, lower UTIs, and cancer. The guideline published by Hanno et al. (2011) was currently the most comprehensive guideline available for the management of IC/PBS and was discussed in greater detail in chapter 2. The algorithm from this guideline is included in Appendix D. The algorithm written by Hanno et al. (2011) included basic management principles and several levels of treatment, implemented in a step-wise fashion or simultaneously based on the clinician's assessment of the patient's condition.

Effective management of IC/PBS depends on accurate diagnosis of the disease. Current literature suggested that IC/PBS is diagnosed and managed in the primary care setting (Patel et al., 2008). The purpose of the guideline published by Hanno et al. (2011) was to provide a clinical framework for the diagnosis and treatment of IC/PBS. The

authors acknowledged that due to a lack of high quality evidence supporting the recommendations in this guideline, further RCTs related to diagnosis of IC/PBS were needed to improve current practices.

Recommendation Evidence

Management of IC/PBS can be difficult and treatment should be tailored to each individual. IC/PBS is a chronic disease and a cure or complete relief from symptoms is not a realistic outcome for patients at this time. Appropriate management of IC/PBS focuses on reduction of symptoms and improvement of quality of life to a level that is acceptable to the patient (Forrest & Mishell, 2009; Sairanen et al., 2009).

Non-Pharmacologic Management.

The AUA guideline by Hanno et al. (2011) stated that the clinical principle treatment of IC/PBS should begin with the most conservative therapy providing adequate control of symptoms to support an acceptable quality of life. A clinical principle is a statement that is widely agreed upon by urologists or other clinicians for which there may or may not be supporting evidence in the medical literature (Hanno et al., 2011). According to the AUA guideline, a clinical principle for first line treatment focuses on pain management, stress reduction, coping techniques, self-care practices, and behavioral modifications that improve symptoms (Hanno et al., 2011). The RCT by Chaiken et al. (1993) demonstrated the effective use of behavior modification for management of symptoms of urgency, frequency and pain related to IC/PBS. Chaiken et al (1993) found that behavior modification does significantly improve functional bladder capacity in women ($p < 0.01$). The findings of Chaiken et al. (1993) were not

corroborated by newer research because more recent studies of behavior modification for the relief of symptoms of urgency, frequency and pain had not been conducted. Rothrock et al. (2003) conducted a case report of 64 women with IC/PBS supporting the statement by Hanno et al. (2011) that coping techniques improve outcomes for women with IC/PBS. Rothrock et al. (2003) found that maladaptive coping strategies were associated with higher levels of depressive symptoms and decreased quality of life in patients with IC/PBS. Self-care practices to improve symptoms of IC/PBS suggested by Hanno et al. (2011) included diet modification and avoidance of foods that are common bladder irritants such as coffee or citrus products. In a case study and non-systematic literature review Shorter (2006) found that diets must be individualized for each patient, as foods that exacerbate symptoms in one woman may not increase symptom flares in another. Foods that were commonly found to increase symptoms were alcoholic beverages, coffee, tea, carbonated beverages, tomatoes, and some spices (Shorter, 2006). However, a case control study by Tettamani et al. (2001) did not support the claim that coffee consumption exacerbates symptoms of IC/PBS. Tettamani et al. (2001) found that coffee consumption was not associated with symptoms of IC/PBS; but tea consumption and smoking were positively associated with symptoms of IC/PBS.

Research supported the recommendation by Hanno et al. (2011) that behavior modifications and coping strategies reduce symptoms in women with IC/PBS (Chaiken, Blaivas, & Blaivas, 1993; Rothrock, Lutgendorf, & Kreder, 2003). However, current literature on the effect of diet on symptoms of IC/PBS was inconclusive with outcomes

showing varying results that are not consistent among all women with IC/PBS (Shorter, 2006; Tettamanti et al., 2011).

Pharmacological Management.

Second line therapy recommended as an option by Hanno et al. (2011), was the use of oral medications; amitriptyline, cimetidine, hydroxyzine or pentosan polysulfate (PPS) for the relief of symptoms associated with IC/PBS. However, administration of these medications was shown to have variable efficacy for individuals. Their administration was associated with minimal adverse effects. An AUA guideline option is a non-directive statement that leaves the decision to take an action up to the individual clinician and patient because the balance between benefits and risks or burden appears to be relatively equal or unclear (Hanno et al., 2011).

The literature found that PPS was effective for the management of IC/PBS and that the side effects of this medication were minimal and that in most patients PPS is well tolerated (Anderson & Perry, 2006; Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sairanen et al., 2009; Sairanen et al., 2005; Sand et al., 2008). Nickel et al. (2005) found that longer duration of PPS and earlier initiation of PPS therapy lead to better patient outcomes (Nickel et al., 2005; Nickel et al., 2009). Based on these findings initiation of PPS as therapy for IC/PBS should be a first line treatment rather than a second line therapy as recommended by Hanno et al. (2011). The use of PPS for the management of IC/PBS was the most extensively studied oral treatment for IC/PBS. PPS is also the only oral medication approved by the FDA for treatment of IC/PBS

(Anderson & Perry, 2006). Several RCTs have examined the use of PPS in management of IC/PBS. Nickel et al. (2005) conducted a RCT on the use of PPS for reduction of symptoms of IC/PBS in women. These researchers found that at the end of the 32 week study, 59 to 67 percent of participants had significant improvement in IC/PBS symptoms, depending on the dose. A secondary analysis of this study found that initiation of PPS within 6 months of diagnosis with IC/PBS improved ICSI scores by an average of 3.97 points compared to an improvement of 2.15 points for women who were started on PPS more than 6 months after diagnosis ($p < 0.0472$) (Nickel, Kaufman, Zhang, Wan, & Sand, 2008). These findings supported the use of PPS for effective management of IC/PBS symptoms in women and demonstrated that earlier initiation of the medication led to better outcomes. In a separate secondary analysis of the RCT by Nickel et al. (2005), Sand et al. (2008) found that 42% of women who were treated with PPS found relief from IC/PBS symptoms. Women treated with PPS were more likely to be pleased with PPS ($p < 0.0001$), more likely to benefit from PPS for IC symptoms ($p < 0.0001$), and more likely to recommend PPS for IC symptoms ($p < 0.046$). These women also felt that PPS provided better relief than previous treatments ($p < 0.0038$) (Sand et al., 2008). A systematic review of RCTs published between 1987 and 2006 examined the treatment of IC/PBS with PPS. In this review Dimitrakov et al. (2007) found, in a pooled analysis of six RCTs and one meta-analysis, that treatment with PPS provided symptom improvement for patients with IC/PBS with a relative risk for symptom improvement of 1.78 (Dimitrakov et al., 2007).

The literature showed that use of the medications amitriptyline, cimetidine, and hydroxyzine alone for management of IC/PBS was not effective (Hill et al., 2008; Unwin, 2011). However, Hanno et al. (2011) recommend the use of Amitriptyline, cimetidine, and hydroxyzine for the management of IC/PBS. Dimitrakove et al (2007), in a systematic review of literature, concluded that there was insufficient evidence to recommend the use of oral pharmacological therapies for the management on IC/PBS other than PPS. A cross-sectional study of 750 patients with IC/PBS found that symptoms of IC/PBS were significantly improved with amitriptyline, phenzopyridine, Prelief and codeine (Hill, Isom-Batz, Panagopoulos, Zakariasen, & Kavalier, 2008). In a literature review Unwin (2011) found that use of amitriptyline for treatment of pain, urgency and frequency associated with IC/PBS was safe and effective. Best results in the management of IC/PBS was using amitriptyline in conjunction with PPS and non-pharmacological management (Unwin, 2011).

Hanno et al. (2011) recommended the use of cimetidine or hydroxyzine as second line treatment for IC/PBS, however, current literature did not support the use of cimetidine, or hydroxyzine for relief of symptoms associated with IC/PBS (Dimitrakov et al., 2007; Unwin, 2011). Amitriptyline may be effective for relief of IC/PBS symptoms, however, studies examining the use of amitriptyline were small and the findings varied. PPS is the only oral medication for the management of IC/PBS that was supported by high quality RCTs and systematic reviews.

As a fifth line approach Hanno et al. (2011) offered the option to use Cyclosporine A for the management of IC/PBS, if other treatments had not provided

adequate symptom control and quality of life or if the clinician and patient agreed that symptoms required this approach. In a RCT comparing the use of PPS and oral cyclosporine A for symptom relief in patients with IC/PBS, Sairanen et al. (2005) found that cyclosporine A was significantly more effective than PPS ($p < 0.001$). However, adverse events associated with cyclosporine A administration were more common and severe than PPS treatment including increased blood pressure and serum creatinine (Sairanen et al., 2009; Sairanen et al., 2005). Cyclosporine A is not approved by the FDA for the management of IC/PBS and clinicians are cautioned that if this treatment is used for IC/PBS, the patient must be monitored closely (Sairanen et al., 2009). While cyclosporine A may be effective, the side effects are more severe than PPS. Currently this treatment is not approved by the FDA, therefore providers must use caution if using this medication for the management of IC/PBS.

Best Practice Recommendations

A comprehensive review of literature published between 2002 and 2013 found that the AUA Guideline by Hanno et al. (2011) is the most comprehensive guideline currently available for the management of IC/PBS. Examination of this guideline and other literature that is currently available addressing the management of IC/PBS in adult women who are not pregnant found that the following recommendations represent the best practice for the use of pharmacological interventions and behavioral interventions for the improvement of IC/PBS symptoms in these women. Each recommendation is given a grade based on the quality and amount of evidence available to support the recommendation. The Scottish Intercollegiate Guidelines Network (2011) grades of

recommendations were used to grade the evidence. Grades of A through D were given; a grade of an A represents the strongest supporting evidence while D is based on expert opinions. A detailed explanation of each letter grade can be found in appendix D (SIGN, 2011).

- Behavioral modification and adequate coping strategies should be first line therapy (Chaiken et al., 1993; Hanno et al., 2011; Rothrock et al., 2003). Hanno et al. (2011) addressed the use of general relaxation, stress management, pain management, self-care and behavior modification as first line treatment; however the authors did not specifically recommend the benefit of learning adequate coping strategies that was found to be effective by Rothrock et al. (2003). Grade C
- Diet modification as part of behavioral modification was not effective. Current literature on the effect of diet on symptoms of IC/PBS was inconclusive with outcomes showing varying results that are not consistent among all women with IC/PBS (Shorter, 2006; Tettamanti et al., 2011). Dietary restrictions were recommended by Hanno et al. (2011) as part of first line therapy, however restrictions increased some patients' stress levels without providing significant relief (Shorter, 2006; Tettamanti et al., 2011). Grade C
- PPS should be offered as a first line therapy for women with IC/PBS (Anderson & Perry, 2006; Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sairanen et al., 2009; Sairanen et al., 2005; Sand et al., 2008). Hanno et al. (2011) included PPS with all other oral medications as second line therapy due to

the potential for minor side effects. However, the literature found that PPS was effective for the management of IC/PBS and that the side effects of this medication were minimal. Most patients tolerated PPS well (Anderson & Perry, 2006; Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sairanen et al., 2009; Sairanen et al., 2005; Sand et al., 2008). Nickel et al. (2005) found that longer duration of PPS and earlier initiation of PPS therapy led to better patient outcomes (Nickel et al., 2005; Nickel et al., 2009). Grade A

- Amitriptyline, Cimetidine and hydroxyzine should not be used alone for the management of IC/PBS. In conjunction with PPS, these may be offered as a second line therapy (Dimitrakov et al., 2007; Hill et al., 2008; Unwin, 2011). Hanno et al. (2011) grouped all oral medications together as second line therapy, these medications should be second line therapy not only due to potential adverse effects but also due to varied effectiveness found in the literature (Dimitrakov et al., 2007). The literature showed that use of the medications amitriptyline, cimetidine, and hydroxyzine alone for management of IC/PBS was not effective, however, use of these medications with PPS showed some benefit (Hill et al., 2008; Unwin, 2011). Grade D
- Cyclosporin A is not recommended for the management of IC/PBS (Sairanen et al., 2009; Sairanen et al., 2005). Hanno et al. (2011) recommended Cyclosporine A as a fifth line treatment with an evidence grade of C. However, the adverse events associated with Cyclosporine A administration were more common and severe than PPS treatment. Adverse events included increased blood pressure

and serum creatinine (Sairanen et al., 2009; Sairanen et al., 2005). Cyclosporine A was not approved by the FDA for the management of IC/PBS and clinicians were cautioned that if this treatment is used for IC/PBS, the patient must be monitored closely (Sairanen et al., 2009). Grade A

Summary

Management of IC/PBS is challenging and patient care should focus on providing adequate relief to the patient with the most conservative treatments possible. The literature showed that behavioral modification and adequate coping strategies significantly improve symptoms and quality of life for women with IC/PBS (Chaiken et al., 1993; Rothrock et al., 2003). While several oral medications were suggested for the management of IC/PBS, the literature did not show that amitptylene, cimetidine, or hydroxyzine significantly improved symptoms of IC/PBS in women; nor improved the quality of life in these patients (Dimitrakov et al., 2007; Hill et al., 2008; Unwin, 2011). PPS is the only oral medication with the FDA indication for treatment of IC/PBS. RCTs and systematic reviews found that PPS significantly improved symptoms of IC/PBS and quality of life with minimal side effects and the medication was generally well tolerated (Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sand et al., 2008). Oral cyclosporine A was effective in the relief of symptoms of IC/PBS, however, the side effects of the medication were common and the risk may out weigh the benefit (Sairanen et al., 2009; Sairanen et al., 2005). Best practice management of IC/PBS begins by setting realistic goals with the patient for adequate symptom control and

quality of life. Behavior modifications and coping strategies should be initiated first then the use of PPS for symptom relief should be considered.

CHAPTER 4

CONCLUSIONS AND RECOMMENDATIONS

This chapter will present recommendations for practice, research, leadership, and policy development for the management of IC/PBS in women. This project has identified best practice recommendations for management of IC/PBS based on a comprehensive systematic review of the available literature. Implications of these recommendations to promote evidence-based practice for the management of IC/PBS could benefit healthcare providers and women with IC/PBS.

Implications for Practice

Currently healthcare providers do not recognize IC/PBS when women initially present with symptoms. The diagnosis of IC/PBS is difficult due to the lack of specific histopathologic changes, unpredictable flares and remissions of symptoms early in the disease progression, and an extreme variability in presenting symptoms among patients (Dell, 2007; Hanno, 2002; Hanno et al., 2011). A survey conducted by Clemens et al. (2010) found that primary care physicians were unfamiliar with IC/PBS and many had erroneous beliefs about the disease. Only 61% of primary care physicians surveyed correctly understood that IC/PBS was not caused by a psychiatric illness and only 67% identified bladder pain or pressure as the hallmark symptom of IC/PBS (Clemens et al., 2010). This survey also found that many physicians are treating patients with IC/PBS

with treatments proven to be ineffective; 33% of primary care providers treated their patients with antibiotics despite negative urine cultures and a lack of response to this treatment (Clemens et al., 2010).

It was estimated that the delay in diagnosis from onset of first symptoms is about five years (Heck, 2007). Misdiagnosis and delayed diagnosis leads to unnecessary diagnostic testing, surgical procedures and a decreased quality of life (Forrest & Moldwin, 2008; Heck, 2007). Earlier recognition and appropriate treatment reduce the negative effects of IC/PBS.

The American Association of Colleges of Nursing (AACN) defined one of the essentials of the advanced practice nurse with a Doctorate in Nursing Practice (DNP) as a strong scientific underpinning for practice (AACN, 2006). A DNP nurse develops a wide knowledge base gleaned from the sciences and the ability to translate that knowledge quickly and effectively into practice for the benefit of patients (AACN, 2006). The advanced practice nurse with a DNP has the unique skill set to translate into practice the current research for the best management of women with IC/PBS. In collaboration with other healthcare providers, the DNP nurse needs to implement the management techniques proven in literature to benefit women with IC/PBS, such as oral PPS and stress management techniques; and discontinue outdated and ineffective treatments such as oral antibiotics and other medications shown to be ineffective. The DNP nurse also participates in the continual gathering and evaluating of current research on the management of IC/PBS and translates new findings into clinical protocols to improve patient outcomes. Consistent use of the management techniques for IC/PBS supported

by high quality evidence and continuing education on evidence based practice guidelines for healthcare providers will lead to better patient outcomes.

Implications for Research

Scholarship and research are the hallmarks of a doctoral level education. DNP nurses participate in scholarship through the translation and application of knowledge and the integration and synthesizing of information into practice (AACN, 2006). Need exists for the advancement of the body of knowledge regarding the management of IC/PBS in women. Current well-designed studies on the effectiveness of non-pharmacological management strategies for IC/PBS are not available. Further study of pharmacological interventions is also needed to better determine the most effective way to manage IC/PBS in women. In addition to participation in gathering new scientific knowledge on the management of IC/PBS, DNP nurses have the opportunity to translate this research into best-practice protocols for diagnosing and managing IC/PBS in primary care and specialty practice. One of the roles of the DNP nurse as a researcher is to collaborate with PhD prepared nurses in discovery research to provide new treatment options for patients. In the practice setting, the DNP nurse enhances research by collecting new data. The DNP nurse partners with other doctoral level practitioners to synthesize and interpret this data and make new treatment recommendations. The DNP prepared nurse adds his/her experience from the clinical setting to tailor recommendations for the practice setting for implementation and improved patient outcomes.

Implications for Leadership

The Essentials of Doctoral Education for Advanced Nursing Practice published by the AACN states that, “doctoral education in nursing is designed to prepare nurses for the highest level of leadership in practice and scientific inquiry.” (2006, p.7). DNP graduates are prepared to develop and evaluate care delivery approaches that meet current and future needs of patient populations based on scientific findings and enhance the quality of health care for populations with whom they work (AACN, 2006). The healthcare provider caring for adult women should be familiar with the best practice for recognizing and managing IC/PBS. The DNP nurse demonstrates leadership in the field by providing education on best practice management of IC/PBS to other healthcare providers to improve quality of care and outcomes for women with IC/PBS.

As evidenced by the study by Clemens et al. (2010), and personal experience, there is a lack of knowledge and understanding of IC/PBS. Primary care providers are not aware of which patients to screen for IC/PBS or how to treat patients that providers suspect have IC/PBS.

Strategies for this project focused on improving policy in two primary care rural settings with a focus on educating providers about IC/PBS diagnosis. Particular attention was given to patients who had been frequently treated for UTIs and either had not had a urine culture done or were treated with an antibiotic despite a negative culture. In these rural health care settings, primary care providers had to begin treatment for IC/PBS and help the patient manage symptoms. Providers were educated on first line treatments of stress reduction and initiation of PPS to improve patients’

symptoms. Providers were receptive to education and implementation of recommendations into practice. After receiving continuing education, providers conducted urine cultures on every woman frequently presenting with symptoms of UTI ruling out the presence of bacteriuria and promoting a possible diagnosis of IC/PBS.

Implications for Policy development

According to the ANCC Essentials for Doctorate Education, DNP graduates must be skilled in working within organizational and policy arenas in addition to the actual provision of patient care (AACN, 2006). DNP nurses are proficient in quality improvement strategies and in creating and sustaining changes in the organization and policy (AACN, 2006). Leadership from DNP nurses in policy development is essential to the nursing profession and the patients they serve (AACN, 2006). The purpose of institutional and practice policies are to ensure best practice, safe practice, optimal patient outcomes and cost-effective treatment of patients. DNP nurses contribute to policy development by serving on development councils and contributing to decisions made through direct involvement or education of others involved in policy development (AACN, 2006). Policy development in the author's primary care practice, related to the management of IC/PBS, is currently in progress. This policy will provide guidance on treatment of IC/PBS, improving patient outcomes.

Summary

IC/PBS is a chronic condition affecting millions of women in the United States that is often unrecognized and undiagnosed (Burkman, 2004; Forrest & Moldwin, 2008). DNP advanced practice nurses are in the unique position to manage IC/PBS in women,

educate patients and other healthcare providers about the disease, contribute to new research, and contribute to the development and implementation of best practice guidelines and policies to improve patient outcomes.

DNP advanced practice providers use the most current literature to improve their practice and patient outcomes. Literature on the management of IC/PBS supported the use of oral PPS for management of IC/PBS (Dimitrakov et al., 2007; Nickel et al., 2005; Nickel et al., 2008; Sand et al., 2008). The literature did not support the use of amitrypyline, cemetidine, or hydroxyzine for management of IC/PBS (Dimitrakov et al., 2007; Hill et al., 2008; Unwin, 2011). Behavior modifications and coping strategies provided some symptom improvement (Chaiken et al., 1993; Rothrock et al., 2003). Best practice management of IC/PBS should focus on setting realistic goals with a patient for an acceptable quality of life, incorporation of behavior medications, appropriate coping strategies and oral PPS. Further research on the management of IC/PBS is needed, particularly of non-pharmacological therapy and oral medications as alternatives to PPS. New research and the development of evidence based protocols for the management of IC/PBS provides many opportunities for DNP advance practice nurses to participate in new research and translation of research into practice.

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APPENDIX A

Table A.1: Evidence Tables

| Brief Reference | Type of study/ Grade | Methods | Threats to validity/ reliability | Findings | Conclusions |
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| (Anderson & Perry, 2006) | Review of literature/ 3 | Authors searched medical literature published in any language since 1980 on pentosan polysulfate. Search engines used were MEDLINE, EMBASE and AdisBase. Results were supplemented with references from the bibliography of published articles. The Search terms used were 'pentosan polysulfate' or 'pentosan polysulfate' and 'interstitial cystitis'. Studies were selected for inclusion based on methods of selection | The strength of the evidence found was not discussed and recommendations were not graded. The authors state that When available large, well-controlled trials were preferred, however, they do not discuss how many of these studies were large well-controlled trials. | PPS is a semi-synthetic, sulfated polysaccharide chemically similar to heparin. The exact pharmacokinetics are not well understood, it is thought that it repairs the GAG layer on the bladder epithelium reducing permeability to toxins from the urine. It may also reduce histamine secretion thereby reducing inflammation. Bioavailability of PPS is very low. Well-designed trials found that compared to | PPS has shown beneficial effect in a large proportion of IC patients. It improves the patients' overall condition and provides pain relief. It is generally well tolerated and side effects are usually mild. Current literature supports the use of PPS as an important option in the treatment of IC. |

| Brief Reference | Type of study/ Grade | Methods | Threats to validity/ reliability | Findings | Conclusions |
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| | | used in the trials. When available large well-controlled trials were preferred. | | placebo PPS was more effective at treating moderate to severe IC. In patients with less severe IC PPS was not significantly different from hydroxyzine and less effective than cyclosporine. Non-comparative studies of long-term treatment show that PPS significantly reduces pain over time. Use of PPS and heparin was shown to be more effective than either alone, however use of PPS and hydroxyzine together is not significantly different than use of either alone. | |

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| (Chaiken et al., 1993) | Case study/3 | <p>42 women previously diagnosed and treated for IC were selected to participate in behavioral therapy for refractory symptoms of urgency, frequency and suprapubic pain related to IC. These women participated in an 8 to 12 week course of 1 45-minute behavioral therapy session per week. Women were asked to keep a voiding journal, inter-voiding interval; number of micturitions per day and a global assessment scale were used to measure effectiveness of therapy. An experienced therapist with training in psychology and lower urinary tract physiology performed therapy. Baseline values for total daytime void volumes, maximum</p> | <p>Data rely on the accuracy of participants to a keep a voiding journal. 16 participants were excluded from the results because of a failure to keep the voiding journal. Behavioral therapy requires highly motivated patients and skilled therapist many IC patients may not comply with the requirements of this therapy. All women participating in this study had tried other treatments for IC such as medications, intravesical instillations, and mechanical interventions, none of which provided lasting relief, these women may be more motivated to complete behavioral therapy than the average IC patient.</p> | <p>21 participants reported that their global assessment scale symptoms were markedly improved, and 16 stated that they were improved. Those who had markedly improved symptoms had an average increase interval between voids of 123 minutes and an average of voiding 6 times per day. The functional bladder capacity increased in 38 of 42 patients ($p<0.01$), inter-voiding interval increased in all patients by an average of 93 minutes ($p<0.01$), the maximum interval increased in 38 of 42 patients ($p<0.01$) and 41 patients</p> | <p>Behavioral therapy does improve global symptoms assessment scores and increases intra voiding intervals, and decreases number of voids per day. This therapy is effective for the highly motivated patient who has access to a skilled therapist. However only a small percentage of patients with IC agree to undergo this treatment, as it is labor intensive.</p> |
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| | | <p>voided volume, mean voided volume, maximum and mean inter-voiding intervals and total number of micturitions were recorded. Post treatment values in the same categories were determined and patients were asked to rate their global results of therapy as markedly improved, improved, unimproved or worse. This data was then analyzed with the student's t test.</p> | | <p>experienced a decrease in the number of micturitions a day by an average of 9 ($p<0.01$).</p> | |
| (Dell, 2007) | Expert opinion/ 4 | <p>Dell presents a review of literature related to the differentiation between UTIs and IC/PBS, and the diagnosis and management of IC/PBS</p> | <p>Dell does not rate the evidence that he has reviewed leaving it hard for the reader to draw their own conclusions as to how reliable the recommendations are.</p> | <p>IC/PBS is a challenge to diagnose as patients have a range of symptoms that overlap with other disorders, such as UTI. May patient s are treated empirically with antibiotics even though their urine</p> | <p>A urine culture is all that is needed to differentiate a UTI from possible IC/PBS. IC/PBS is more common than once thought, patient care can be improved by completing a urine culture on patients presenting with irritate voiding symptoms.</p> |

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| | | | | cultures are negative and they are later diagnosed with IC/PBS | Management should focus on a multimodal approach combining oral and intravesical pharmacological treatment with diet and lifestyle modification and other non-pharmacological potions, including stress reduction, exercise, bladder training, biofeedback physical therapy. |
| (Dell & Butrick, 2006) | Literature review and expert opinion/ 4 | The method of literature review was not discussed in this publication. | The method of literature review was not discussed, the quality of articles found and used in the article were not graded making it difficult to judge the quality of these recommendations. | The exact cause of IC is unknown making finding a targeted cure impossible. Recent experience demonstrates that symptoms can be managed. A scientifically rational approach is a multimodal treatment strategy directed toward treatment of the 3 components considered key to the pathogenesis of IC. The dysfunctional | Non-pharmacologic therapies that can be combined with medications to enhance outcomes include diet modification to avoid foods high in potassium and acid. In patients with pelvic pain associated with concomitant pelvic floor muscle tenderness and spasm restoration of normal tone and function though physical therapy and home |

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| | | | | <p>bladder epithelium, associated allergies, and neural upregulation. The benefits of pharmacologic interventions can be enhanced with dietary changes, physical therapy and bladder retraining.</p> | <p>exercise to realign the sacrum and ileum by internal direct manual therapy of the pelvic floor muscles is helpful. Bladder training and biofeedback are also helpful. Pharmacologic treatment should start with the only FDA approved medication for IC pentosan poly sulfate sodium (PPS). PPS appears to replenish the defective mucous layer and restore bladder integrity it is currently the most effective treatment for IC. Other pharmacologic treatments that may be used in conjunction with PPS include antihistamines, TCAs, analgesics, anticholinergics, estrogen creams and cycle suppression with continuous OCPs, and skeletal muscle relaxants.</p> |
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| (Dimitrakov et al., 2007) | Systematic review of RCT/ 1++ | <p>RCT for pharmacologic treatment of patients with IC diagnosed based on the NIDDK definition of IC or operational criteria were included in the review. Nine databases were searched including Pubmed, CINAHL, Web of Science the Cochrane Collaboration Reviews and others. Terms included Interstitial cystitis, and painful bladder syndrome. Other key words were those that described the publication as randomized, double blind, random allocation, placebo, clinical trial and comparative study. All studies were limited to those published in English and those that studied adults. Only trials for PPS had sufficient numbers to allow a pooled analysis. A total of 1470 adult</p> | <p>The patient sample was heterogeneous, possibly making generalization to the general population difficult. There was considerable variability in the definition of symptoms and in outcome assessments among the RCTs reviewed.</p> | <p>A pooled estimate of the effect of PPS therapy suggests benefit from this therapy with a relative risk of 1.78 for patient-reported improvement in symptoms. Current evidence also suggests that dimethyl sulfoxide and amitriptyline are effective therapy for IC. Hydroxyzine, intravesical bacilli Calmette-Guerin and resiniferatozin therapies failed to show significant efficacy.</p> | <p>PPS therapy has shown modest improvement in symptoms of IC. There is insufficient evidence to recommend other pharmacological therapies.</p> |
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| | | patients from 21 RCT were used. | | | |
| (Forrest & Dell, 2007) | Clinical article/ 4 | Methods of literature review are not discussed | This article is based on a review of literature and expert opinion. The strength of the literature and the qualification of the authors are not presented. | PCPs, urologists, and OB/GYNs have the opportunity to detect and provide effective management of IC in its early stages. Treatment should include counseling on lifestyle modification to avoid triggers such as high potassium foods, and allergens. First line therapy is a combination of oral medications including PPS. Preliminary data shows that intravesical treatment may help relieve symptoms in the period before PPS reaches its full effect. Patients should be reevaluated between 1 and 3 months of starting treatment. Biofeedback and neurostimulation have also been shown to be effective. | Management of IC is multimodal using a multi drug oral regimen including PPS. And other therapies patients may require including intravesical instillations, biofeedback, and neurostimulation. |

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| (Forrest & Mishell, 2009) | Expert opinion/4 | Recent literature was reviewed by a panel of leaders in urology, gynecology, urogynecology and general women's health to reach a consensus and formulate algorithms for diagnosing and treating IC/PBS | The paper is based on the consensus of experts and the "recent literature reviewed" is not described or ranked. | IC is the cause of a large portion of chronic pelvic pain (CPP), suggesting that the diagnosis of IC should be a diagnosis of inclusion, and should be considered at the same time as other common diagnoses rather than only when other causes have been ruled out. Primary goals of treatment are relief of pain and improvement of quality of life. The factor that correlated most strongly with favorable therapeutic response was duration of symptoms prior to treatment; early treatment provides better outcomes. | Many women with CPP are symptomatic for longer than necessary because of missed or late diagnosis. IC should be considered as a source of CPP early in the diagnostic process to prevent unnecessary gynecologic surgery. Clear diagnostic criteria for IC must be identified; the hope of the expert panel is that the algorithms provided here serve that purpose. PPS has undergone prospective randomized trials and was shown to have significant symptom improvement over placebo. 90% of patients report that certain foods exacerbated symptoms. Multimodal treatment should include a behavioral component to optimize |
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| (Forrest & Moldwin, 2008) | Review of literature and expert opinion/4 | Experts in management of IC/PBS discussed tools available to diagnose and treat IC and the advantages and disadvantages of each approach. Researchers also reviewed literature for relevant articles on the background, diagnosis, and treatment of IC with a focus on the importance of early intervention. | The authors do not discuss the qualifications of the experts who contributed to this review. They also do not discuss the quality of the literature available and reviewed. | Diagnostic options for IC include history and physical exam, lab evaluations, symptom screening tools, cystoscopy with hydrodistention, bladder biopsy, PST, ABC, urodynamics and urinary markers. Treatment options include oral and intravesical medications, dietary modifications and physical therapy. Patient follow –up is an important opportunity for education. | Most treatment options take time to take full effect encouragement to adhere to treatment plan is important. Non-pharmacological treatments such as dietary modification, stress and anxiety reduction, exercise, physical therapy, counseling, bladder training and pelvic floor rehabilitation can be beneficial and enhance pharmacologic management. Regardless of treatment approach early identification of IC improves patient outcomes. |
| (Hanno et al., 2011) | Guideline Guideline AGREE Score: Scope & purpose=78% Stakeholder | A committee of urologist, nurses and other clinicians with specific expertise on IC/PBS developed the AUA guideline. The committee conducted a systematic review of | Only the database of MEDLINE was searched, possibly limiting the search and excluding some valuable studies. Because of a lack of evidence expert opinion is used to make some | First through sixth line treatments were recommended. A treatment algorithm was provided to summarize these findings. First line treatment is | IC is best managed through a logical algorithm such as the one presented in this paper. Diagnosis and treatment options can be expected to change as there is currently |

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| | <p>involvement=67%</p> <p>Rigor= 71%</p> <p>Clarity=92%</p> <p>Applicability=11%</p> <p>Editorial independence=67%</p> | <p>MEDLINE of publications in English published between 1/1/1983 and 7/22/2009. Meta-analysis of Randomized controlled trials and systematic review were used to analyze the evidence. Grades of A, B or C were given to bodies of evidence to indicate the strength of the evidence available for particular recommendations. Grade A were well-conducted RCTs or very strong observational studies; grade B consisted of RCTs with some weakness of procedure or generalizability or strong observational studies; Observational studies that are inconsistent, have small sample sizes or have other problems that confound interpretation of data were graded</p> | <p>recommendations rather than systematic review of literature. By limiting the included studies to those conducted in the US it is possible that valid treatments that should be considered have been excluded. The cost of these recommendations is not address the authors also do not provide monitoring criteria for audit because this is inherently difficult with this disease process. They also do not provide a process for revision/update but simply state that the guideline will be updated, as more research is available. The panel chosen to write this guideline is made up of experts in Urology and IC/PBS; there is a full disclosure of any conflicts of interest.</p> | <p>considered to be general relaxation and stress management, pain management, education and behavior modification. Pain management should be addressed at all stages of treatment.</p> | <p>little evidence on the subject and as more evidence is provided recommendations will change. No single treatment is found effective for the majority of IC patients. First line treatment is education, self-care practices and behavioral modifications such as diet changes, stress management and pelvic floor muscle relaxation and bladder training. PPS and other prescription medications are considered second line treatment because administration is associated with minor adverse events and efficacy for individuals is unpredictable.</p> |
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| | | <p>level C. Insufficient evidence was found on the diagnosis of IC/PBS recommendations were made based on clinical principles and expert opinions. The AUA defines clinical principle as a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature. Expert opinion is defined as a statement that is achieved by consensus of the committee based on members clinical training, experience, knowledge and judgment for which there is no evidence. The Cochrane Risk of Bias tool was used to assess individual studies that were RCTs. Studies addressing treatments</p> | | | |
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| | | not available in the US using herbal supplements and information collapsed across multiple interventions were excluded. | | | |
| (Hill et al., 2008) | Cross sectional survey/3 | 750 patient diagnosed with IC completed a computerized Internet survey that was linked on the Interstitial Cystitis network, national Women's Health Network and Our Bodies Ourselves websites. The survey questioned patients about demographics, symptoms, co morbidities, treatments and perceived treatment outcomes. Statistical analysis was conducted using SPSS statistical software, descriptive statistics were calculated and person chi-squared tests were used to compare the percentage of patients | Survey studies are subject to risks involving inaccurate self-reporting. | Hydrodistention, intravesicular therapy, and urethral dilation were the most common invasive treatments used. Of these procedures 27-49.8% of patients felt no effect, 24.4-45.3% were improved, and 25.9-30.7% felt symptoms worsened. 2.7% (395) of the 750 individuals surveyed had taken PPS 53.4% found that the medication improved IC symptoms, 3.8% felt that it made symptoms worse, 29.9% felt that it did not have any effect and 12.9% of patients felt PPS side effects | The majority of patient reported that medications improved their condition. Medical therapy is perceived to be better than invasive therapy for IC. Medications that were perceived to improve IC symptoms include PPS, calcium glycerophosphate (Prelief OTC), Amitriptyline, phenazopyridine, and Codine. Vistaril, tolterodine, oxybutynin, oxybutyninXL, and diphenhydramine appear to have no significant effect on IC symptoms. |

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| | | who fell into each of the three groups based on their perceptions of each treatment: improved, no effect or made worse. | | were intolerable ($P<0.001$). Other medications that significantly improved patients' perception of IC symptoms include phenazopyridine, calcium glycerophosphate (Prelief), amitriptyline, and codeine. Vistaril, tolterodine, oxybutynin, oxybutyninXL, and diphenhydramine were reported by the majority of patients to have no effect on IC symptoms ($p<0.001$). | |
| (Nickel et al., 2005) | RCT, double-blind/ 1+ | Three dosages of pentosan polysulfate sodium (PPS) were evaluated in a randomized, double blind, double-dummy, parallel-group multicenter 32-week study. 380 adults with a diagnosis of IC were | The completion rate of the study was 60%, not unexpected by the authors given the length of the study. There was not a comparable placebo group. Most of the patients who participated in this study had moderate to sever | No statistically significant difference in response among the three dosages of PPS was found. There was significant improvement in the average ICSI scores ($p<0.001$) over the 32-week period in all | Dosages of 300mg, 600mg, and 900mg of PPS all show clinically significant results in reduction of symptoms of IC, however the difference between the dosage groups is not significant. Duration of therapy appears to be |

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| | | randomly assigned to dosage groups of 300 mg, 600 mg or 900 mg of PPS. Patient symptoms at base line at points during the study and at the end of the 32 weeks were evaluated using the O'Leary-Sant IC Symptom Index (ICSI) and the Patient's Overall Rating Symptom Index (PORIS). Results were analyzed using a two sample t test and chi square analyses with a significance level of $\alpha=0.05$. | symptoms of IC and a better understanding of the treatment effect of PPS may be gained by studying patients in early stages of IC. | dosage groups. Earliest improvement in ICSI scores was seen in 4 weeks. Patients with severe baseline symptoms responded better to 600mg dose of PPS ($p=0.028$). 17-23% of participants saw improvement in ICSI scores in 4 weeks by the end of the study (32 weeks) 59 to 67% found improvement of symptoms. | more important that the dosage of PPS. Over half of study participants found relief by the end of the 32-week period even if they did not have significant symptom relief at the four-week measurement. Even though this study lacks a control group and participants were IC patients with moderate to severe symptoms the methodology of this trial provides strong scientific evidence to support therapy including PPS as beneficial for the relief of symptoms in women with IC. |
| (Nickel et al., 2008) | Secondary analysis of RCT/2- | Retrospective secondary analysis of a previously published 32-week multi center randomized, double blind. A subset of 128 women who received PPS 300mg/day were analyzed in this study. | The original RCT did not have a placebo group. The time from diagnosis to initiation of PPS was used to evaluate time until initiation of treatment and is not representative of time since IC symptoms | The ICSI score for the early treatment group had an average improvement score of 3.97 points compared to an improvement of 2.15 points in the late treatment group ($p=0.0472$). The ICPI | Early recognition of IC and prompt initiation of treatment may lead to more improvement in IC symptoms and response to therapy. Individuals treated with PPS within 6 months of diagnosis showed |

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| | | <p>Participants were further sub-categorized as receiving early treatment with PPS (initiation within 6 months of diagnosis with IC) and late treatment (initiation of treatment 24 months or more after diagnosis of IC). Outcome measure included the ICSI and the ICPI. Scores from the ICSI and ICPI were compared using an analysis of covariance ANCOVA model that included the category for time since IC diagnosis as a factor and baseline score as a covariate. All statistical tests were performed at a 5% significance level.</p> | <p>began, especially since many patients with IC suffer from symptoms for months or years before diagnosis. Both the early and late treatment groups had moderate to severe IC symptoms at baseline making it difficult to generalize to patients who experience mild IC symptoms. The majority of patients had also received at least one IC medication before enrollment in the study, which may have created an unknown bias.</p> | <p>showed similar results with an average improvement of 3.94 points from baseline in the early treatment group and 1.77 points in the late treatment group ($p=0.0117$). This exploratory analysis suggests that subjects with IC benefit from earlier initiation of PPS therapy. Those who received PPS within 6 months of diagnosis showed significantly greater improvement in both ICSI and ICPI scores.</p> | <p>significant improvement in symptoms scores and symptom bother scores compared to those who did not receive PPS until 24 months or more after diagnosis. Earlier initiation of therapy for IC may provide more benefit to patients diagnosed with IC. Early diagnosis and treatment may be the key to better management of IC and maybe prevention and progression of the disease.</p> |
| (Onwude, 2009) | Literature review/ 4 | <p>Externally peer reviewed clinical article published in the <i>British Medical Journal</i> with the goal of highlighting areas of practice where management lacks supporting evidence.</p> | <p>The method of literature review is not discussed. The quality of literature available is not discussed, the author does note that the quantity of quality evidence is lacking.</p> | <p>IC currently has no standardized treatment and current randomized drug studies offer conflicting results.</p> | <p>A systematic review of oral treatments for IC is needed. Patients and clinicians should understand the limitations of evidence for current treatments and set realistic</p> |

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| | | | | | treatment goals. |
| (Parsons, 2002) | Non-systematic review of literature and expert opinion/4 | Discussion of IC through review of literature and author's experience as an expert in treating IC for 20 years. | The rigor to which the literature was reviewed was not discussed. The author relies on 20 years of experience and the treatment of more than 5,000 IC patients to give himself credibility as an expert. | IC is a relatively common disorder that can be recognized in its early stages and treated with a high measure of success. | Treatment should be based on restoring epithelial function with heparinoids such as intravesicular heparin or oral PPS; modulating neural activity, with TCAs; and controlling allergies. Oral PPS had been effective in treating IC, duration of treatment is more important than dose. Young patients 18-30 generally have good symptom improvement with oral PPS over 2-4 months. |
| (Parsons, 2006) | Expert opinion/ 4 | The article summarizes the latest advances in medical treatment of IC based on opinions of experts in the field and their experiences in practice. | This article is based on clinicians' experience in treating women with IC rather than rigorously designed clinical trials. | Most individuals are affected by a mild to moderate form of IC that responds to treatment. A heparinoid-based multi modal medical regimen can effectively control symptoms and address disease pathology. Intravesical solutions | PPS has been shown to successfully treat IC in RCT however these studies do not explore the added benefit of longer duration of treatment and use with ancillary treatments. Duration of PPS treatment is at least as important as dose. Heparinoid therapies do not treat the |

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| | | | | are new and promising adjunctive therapies that can offer immediate symptom relief in flares. | symptoms of IC they correct the dysfunction of the epithelial lining of the bladder. Successful management of IC is achieved through multimodal therapy with heparinoid therapy. |
| (Quillin & Erickson, 2012) | Review literature and expert opinion/ 4 | The authors review the AUA guideline on the diagnosis and treatment of interstitial cystitis/bladder pain syndrome and comments on the practical implementation of the guideline and the most recent research. | Strength of other literature reviewed is not discussed. Very little guidance is added to treatment approach other than what is offered by the AUA guideline itself. | <p>Treatment should progress from conservative to more invasive therapies with the goal of attaining acceptable quality of life.</p> <p>Assessment of symptom level and reassessment post intervention evaluates efficacy.</p> <p>Concurrent treatments may be used if in the patient's best interest.</p> <p>Pain management should be continually</p> | <p>Diagnosis of IC/PBS is now made based on history, physical exam, frequency-volume chart, UA, and culture not on cystoscopy or urodynamics.</p> <p>Treatment focuses on education, diet, and stress management. Oral medications and bladder instillations should be considered second line therapy and side effects and polypharmacy should be avoided.</p> |

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| | | | | <p>assessed.</p> <p>Self care practices and behavioral modification should be discussed and implemented first.</p> <p>Amitriptyline, cimetidine, hydroxyzine, or PPS may be administered as second-line oral medications.</p> | |
| (Rosamilia, 2005) | Clinical article/ 4 | The methods of literature review were not discussed in this article. The author does make treatment recommendations and gives each recommendation a grade, however she does not define her grading system or discuss her evidence. | The lack of a methods section makes it difficult to determine the strength of evidence reviewed for these clinical recommendations. | This article reviews the definition, diagnosis and etiology of IC for the clinician and provides graded recommendations for management including physical therapy, behavior modification, diet manipulation, oral therapy, and intravesical therapy. | Behavior modification, physical therapy and dietary manipulation are all offered as treatments for IC, however the author does not provide a grade for these recommendations. Treatment with PPS and Amitriptyline received a grade B recommendation, and evidence for treatment with Hydroxysine, Cimetidine, immunoregulators, antibiotics, |

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| | | | | | cyclosporine and analgesics was limited leading to a grade D recommendation. |
| (Rosenberg, Newman, et al., 2007) | Clinical article/ 4 | Methods of collection of literature are not discussed. | Unable to determine the strength of the data used to complete this article. | Over time IC/PBS can become debilitating, and result in limitations to patient's personal and professional life. Patients with IC/PBS are 5 times more likely to be treated for an emotional disorder than those without IC. The cornerstone of treatment is behavioral therapy. This included educating patients about symptoms, behavioral modification to decrease urgency and frequency, physical therapy to release trigger points, stress reduction, and diet modification. Multimodal pharmacotherapy | IC has a higher prevalence that once realized. IC/PBS has a significant impact on the quality of life. Early identification and initiation of therapy leads to better outcomes. Multimodal therapy including behavioral therapy and multiple drugs are the standard treatments. |

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| | | | | consists of PPS, hydroxyzine, and Amitriptyline. | |
| (Rothrock et al., 2003) | Case reports/3 | 64 women with IC were recruited from the department of urology and the participating institution. All were diagnosed with IC based on the NIDDK guidelines. Participants completed questionnaires assessing depression, quality of life, coping, and symptom severity and a standardized semi-structured depression interview. Descriptive statistical analysis was performed for demographic variables. For each dependent variable regression models were constructed to test the relationships among coping strategies, quality of life and depression. Age and symptom severity were covariates in these | 89.1% of the sample was white and the majority of participants were high school graduates or higher level of education, this sample may not be representative of the general population of women with IC. The use of the NIDDK guidelines for diagnosis of IC is considered to be too restrictive for clinical practice. Women in this study may differ in symptom severity from the average women with IC because they meet these strict criteria for diagnosis. | Age and symptom severity were not associated with depressive symptoms or mental health. However, greater catastrophizing was related to more severe symptoms on all measures of mental health ($p<0.05$). Venting was associated with more depressive symptoms ($p<0.01$) while seeking instrumental support was associated with a decrease in depressive symptoms ($p<0.01$). Younger age ($p<0.05$) and increased symptoms severity ($p<0.001$) were significantly associated with increased pain. | Maladaptive coping strategies are associated with higher levels of depressive symptoms and decreased quality of life in patients with IC. Psychosocial interventions aimed at increasing adaptive coping may improve outcomes for women with IC. |

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| | | models. All analyses controlled for age. | | | |
| (Sairanen et al., 2005) | Randomized Control trial/1+ | 64 patients meeting the NIDDK criteria for diagnosis with IC were enrolled in a randomized prospective study. Participates were randomly assigned to treatment groups with 1.5 mg/kg CyA BID or 100mg of PPS TID for a 6 month period. Daily micturition frequency and ICSI and ICPI were used to evaluate treatment success. Baseline factors were compared with t test and the Mann-Whitney rank sum test, and differences between treatment outcomes were calculated with the Mann-Whitney rank sum test. | The NIDDK criteria for IC is very restrictive and this study may not be representative of how all IC patients would react to treatment, particularly those with early onset, mild symptoms. Sample size was relatively small 29 patients completing the study in each treatment group. | Reduction of micturition frequency in 24 hours by 50% was not seen in any of the patients in the PPS treatment group, and in 11 (34%) of patients in the CyA group ($p<0.001$). CyA was also significantly more effective than PPS in all other parameters measured ($p<0.001$). | Researchers state that PPS has not been found effective for IC patients meeting the NIDDK criteria for diagnosis, however, it is possible that PPS works better for patients with a milder form of IC and in earlier stages. CyA treatment is recommended for patients with severe IC meeting the NIDDK criteria, particularly those who have failed other treatments. Careful follow up including regular monitoring of BP and serum creatinine is mandatory. |

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| (Sairanen et al., 2009) | Second analysis of Randomized control trial/1- | 2 consecutive studies of treatment for IC/PBS were conducted. One compared 75 patients with IC were randomized into either the DMSO intravesicular treatment group or the BCG intravesicular treatment group. The second study 64 patients were randomized into either oral cyclosporine A treatment group or PPS treatment group. All patients included had to meet NIDDK criteria for diagnosis with IC. QOL was evaluated with a 30-item questionnaire. Questionnaire results were evaluated for each treatment group using the Wilcoxon rank sum test. A one-way ANOVA was used to evaluate the similarity of baseline characteristics of treatment arms. | Self reported questionnaires are always subject to bias. Also treatment groups were relatively small. The use of NIDDK criteria for diagnosis with IC may have limited inclusion of patients with IC and limit the study's ability to be generalized to the larger population of women with IC. | All patients who showed a response to their specific treatment had an improved score on QOL questionnaires. CyA treatment group had more improvement in emotional well-being, social functioning, activity limitation and physical capacity than PPS ($p<0.001$). More patients responded to DMSO than BCG ($p<0.01$), but results on QOL questionnaires were equal after either treatment. | The health related quality of life questionnaire could be used to evaluate QOL in patients with IC. It has never been used to evaluate IC/PBS patients prior to this study. Treatment of IC has a significant effect on QOL and QOL can be used to evaluate success of treatment. A QOL questionnaire specific to IC needs to be developed and validated. CyA therapy has a greater impact on the majority of the categories of QOL measurements than PPS. |
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| (Sand et al., 2008) | Secondary analysis of RCT/2- | Retrospective secondary analysis of a previously published 32-week multi center randomized, double blind, parallel-group clinical trial of 380 women. A subset of 128 women who received PPS 300mg/day were analyzed for treatment response using they O'Leary-Sant ICSI and a treatment satisfaction questionnaire. Women were labeled as responding to PPS treatment if they had a greater than or equal to 30% reeducation in the ICSI score from baseline. | The original RCT did not have a placebo group and the treatment satisfaction questionnaire is not a validated instrument. However the O'Leary-Sant ICSI is validated for the evaluation of IC symptoms. 91% of subjects were women with moderate or sever symptoms at baseline, making it difficult to generalize this data to a population of IC patients with mild symptoms. The sub-sample from the original RCT analyzed in this study was relatively small (n=128). | 49 women (42%) with a greater than 30% reduction in ICSI score from baseline were identified as responders to PPS treatment. These women were more likely to be pleased with PPS for treatment of IC symptoms ($p<0.00101$), to have benefitted from PPS ($p<0.0001$) and to recommend PPS to other patients with similar symptoms ($p=0.0466$). 79% of responders found that PPS provided better relief than other treatments tried ($p=0.0038$). Among all subjects more than 70% reported a benefit from PPS at the end of the treatment period, even if they were not identified as | 70% of subjects reported a benefit from PPS including more than a third of those classified as non-responders. Many participants also reported greater symptom relief with PPS compared to previous treatments for IC symptoms. A significantly higher rate of symptom reduction and satisfaction was reported with PPS therapy. PPS therapy has a significant positive correlation between ICSI score and the patient response score on the individual questions in the patient treatment questionnaire. |
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| | | | | responders. This suggests that even non-responders would have ICSI scores showing a trend toward improvement. A substantial proportion of non-responders also reported that they relief that they found with PPS was greater than the relief that they had found with previous treatments for IC. | |
| (Schmid et al., 2011) | Cohort study/ 2- | 69 female patients diagnosed with IC based on the NIDDK standards and histories of unsuccessful treatment were included. Patients were evaluated prior to treatment and two weeks after each step in the treatment algorithm for sexual functioning, and quality of life. If a patient was satisfied with current treatment it was | Using the NIDDK criteria may limit the number and type of IC patients that were included in the study. In addition using patients who had histories of failures with other treatments might suggest that these patients have more severe symptoms that the general population of IC patients. | Researchers found that a stepwise approach to management if symptoms with tetracycline, oral steroids, and antihistamines significantly improved sexual function and quality of life in women with IC/PBS. VAS scores for pain improved significantly after receiving | This study shows that a stepwise approach to therapy with tetracycline, bladder instillation with heparin/local anesthetic, oral steroids, antihistamines, and DMSO instillation significantly improved sexual function and quality of life in IC patients. Improvement in all domains of sexual |

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| | | considered a success and the patient did not progress to the next step of the algorithm, if the patient continued to have symptoms the next step was implemented. The King's Health Questionnaire was used to assess quality of life and the visual analogue scale (VAS) 0-10 was used to assess symptom bother. A two-tailed t test was performed to compare scores before and after treatment. | | treatment ($p<0.001$), as did nocturia ($p<0.01$) and frequency ($p<0.01$). However, Urgency was not significantly improved using this treatment algorithm ($p=0.09$). All domains of the King's Health Questionnaire showed significant improvement ($p<0.001$) with the exception of incontinence impact ($p=0.227$). | function and quality of life cannot be achieved. Long-term follow-up and research on the etiology of IC needs to be conducted to determine efficient therapy. |
| (Shorter, 2006) | Expert opinion with case study/ 4 | This article presents a case study and a summary of the literature about the role of diet in the management of IC. Which as the author admits is limited to anecdotal reports by patients and experts. | The author does not describe her search of the evidence therefore it is hard to grade the strength of her recommendations. Based the author's own report high quality evidence to support diet modifications in IC appears to be lacking. | Data gathered from patients and experts on dietary changes affect on IC symptoms is anecdotal. However, it does show that eliminating certain foods does decrease pain associated with IC in most patients. Dietary treatment is complicated because | There are limited studies on the effect of diet on IC. However, the majority of IC patients have found that certain foods can exacerbate symptoms. The IC association (ICA) has created an IC diet based on anecdotal information from patients and urologist. Foods that are |

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| | | | | it must be individualized and requires keeping a food intake and voiding diary. Foods should be eliminated and then systematically reintroduced to determine which are the offending items. A concern is that by eliminating foods or whole food groups patients may become deficient in some nutrients. | commonly found to exacerbate symptoms include alcoholic beverages, coffee, tea, carbonated beverages, tomatoes, and certain spices. Diets should be individualized and patients should be careful not to eliminate too many foods as that may cause deficiencies in essential nutrients. |
| (Tettamanti et al., 2011) | Case control twin study/ 2- | Female twins with IC were matched with healthy twin controls. Logistical regression models with a 95% confidence interval were used to evaluate the effect of smoking, coffee and tea consumption on symptoms of IC. | Twin controls were used to minimize confounding factors. Disease and exposure are measured at the same time; therefore conclusions about whether the exposure preceded or resulted from the disease cannot be made. | Smoking currently or formerly and tea consumption were associated with significantly higher cases of IC symptoms. Smoking as a risk factor was confounded by familial factors. Coffee consumption was not associated with a higher risk of IC symptoms. | Tea and smoking are positively associated with IC but the association of smoking with IC is likely to be confounded by genetic factors. The association with tea consumption is not confounded by familial factors. Coffee consumption does not have a significant association with IC symptoms. |

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| (Theoharides, 2007) | Literature review/4 | The methods used to conduct this literature review are not discussed. | Inclusion and exclusion criteria of articles used for this review are not provided. Neither is a discussion of the strength of the literature available. Studies reviewed are referenced and described briefly; comments about the strength of individual studies are discussed briefly. However, the reader must draw his/her own conclusion about the strength of body of literature reviewed. | There is no benefit in the form of pain relief from the practice of raising the pH of urine through diet modifications or supplements. Clinical trials to date have used adult patients with varying degrees of severity of IC symptoms and durations of the disease, making it difficult to draw definitive conclusions about the treatments studied. Many of the studies that have been conducted are small and the results should be considered suggestive not conclusive. | There is no curative treatment available for IC. Currently the available literature on definitive treatment for IC is lacking. Intravesical DMSO, oral amitriptyline, PPS and hydroxyzine have variable results. The most successful treatment is likely with a combination of these treatments. |
| (Unwin, 2011) | Review of literature/3 | The author does not discuss details of the literature search process. However, each recommendation is rated based on the | This is a summary of current literature without recommendations made by the author. Threats to validity are related to | IC/PBS is considered in the patient the otherwise unexplained pelvic area pain, urinary frequency and | After establishing diagnosis PPS is a baseline treatment additional multimodal treatments can be used as indicated. |

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| | | strength of the evidence, for example a rating of an A is, “consistent quality patient oriented evidence” and C is based on, “consensus disease oriented evidence, usually expert opinions” | the fact that the method of literature review is unavailable. | urgency, diagnosis is confirmed with cystoscopy. Oral therapy with PPS and amitriptyline and bladder installation of DMSO are the cornerstones of treatment. | Amitriptyline is safe and effective for pain relief. Non-pharmacologic strategies such as bladder training, diet change, counseling, and physical therapy may be helpful but have not been studied in clinical trials. |
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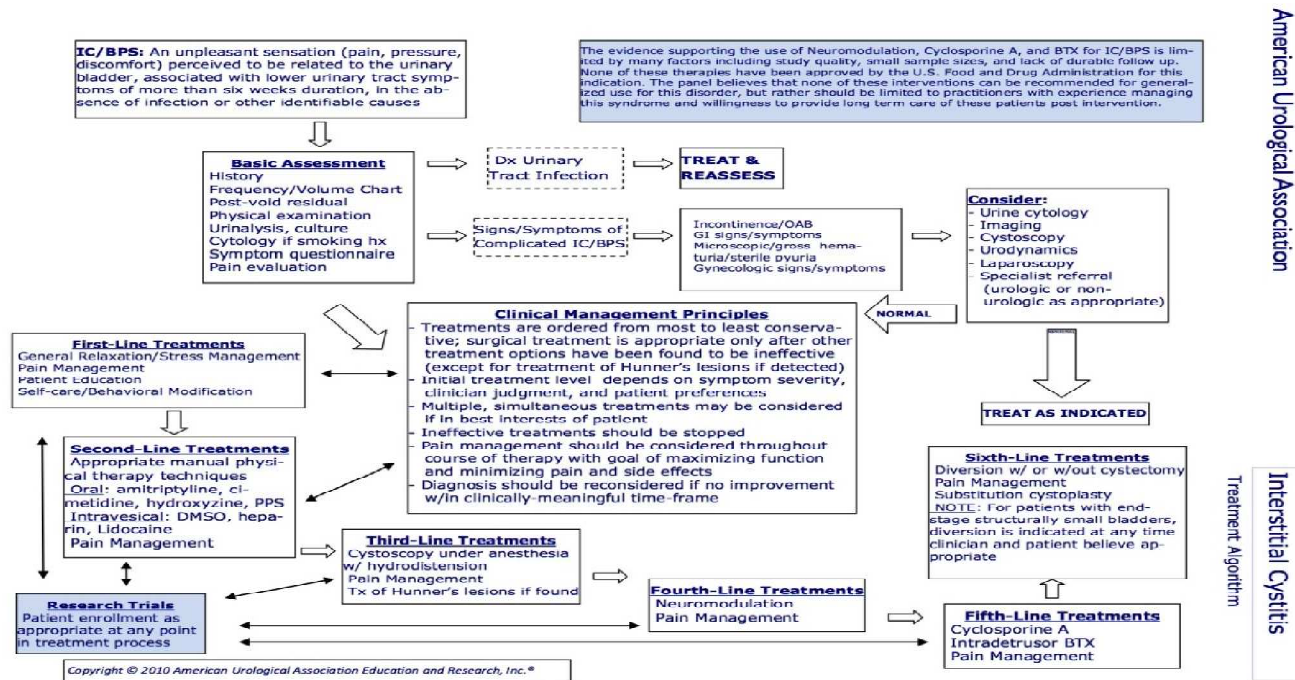
APPENDIX B

Table B.1: SIGN 50 Levels of Evidence

| Levels of Evidence | |
|--------------------|---|
| 1++ | High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias |
| 1- | Meta-analysis, systematic reviews, or RCTs with a high risk of bias |
| 2++ | High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal |
| 2+ | Well-conducted case control or cohort studies with a low risk of confounding or bias and moderate probability that the relationship is causal. |
| 2- | Case control or cohort studies with a high risk of confounding or bias and significant risk that the relationship is not causal |
| 3 | Non-analytic studies, example: case reports, case series |
| 4 | Expert opinion |

(SIGN, 2011)

APPENDIX C



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Figure C.1: AUA Guideline Algorithm

Resent-From: thomasa6@email.sc.edu
From: "Folmer, Michael" <mfolmer@auanet.org> 
Subject: Permission request - Interstitial cystitis
Date: April 12, 2013 12:04:51 PM EDT
To: "LANGFORD, AMANDA" <thomasa6@email.sc.edu>

Dear Ms. Langford,

Thank you for your request. You have permission to use the Interstitial Cystitis treatment algorithm for your purposes (The algorithm would be included in the appendix as a reference for the reader).

Please cite the source.

Interstitial Cystitis (2011)

Hanno, P. M., Burks, D. A., Clemens, J. Q., Dmochowski, R. R., Erickson, D. FitzGerald, M. P., Forrest, J. B., Gordon, B., Gray, M., Mayer, R. D., Newman, D., Nyberg Jr., L., Payne, C. K., Wessellmann, U., Faraday, M. M.:

Guideline on the Diagnosis and Treatment of Interstitial Cystitis/Bladder Pain Syndrome (2011). American Urological Association Education and Research, Inc., ©2011

<http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines.cfm?sub=ic-bps>

Mike

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From: LANGFORD, AMANDA [<mailto:thomasa6@email.sc.edu>]

Sent: Thursday, April 11, 2013 11:11 AM

To: Urology Care Foundation

Subject: Permission to use content

To whom it may concern:

I am a Doctorate of Nursing Practice Student at the University of South Carolina. I am completing an evidenced based practice project on the best practice for managing IC in adult women. I would like permission to use the algorithm included in the AUA guideline by Hanno et al. (2011). The pdf is found at <http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines.cfm?sub=ic-bps>. The algorithm would be included in the appendix as a reference for the reader. This project is for academic purposes and not for publication. Please email at thomasa6@email.sc.edu me and let me know if I have permission to include the algorithm.

Thank you,

APPENDIX D

Table D.1: SIGN 50 Grades of Recommendations

| Grade | Explanation |
|-------|--|
| A | At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population. Or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results. |
| B | A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ |
| C | A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+ |

(SIGN, 2011)